Atty. Dkt. No. 028622-0130

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Nicholas BARDEN et al.
Title:	MEANS AND METHODS FOR DIAGNOSING AND TREATING AFFECTIVE DISORDERS
Appl. No.:	10/825,593
Filing Date:	04/16/2004
Examiner:	Michael D. Pak
Art Unit:	1646
Confirmation No.	7794

DECLARATION UNDER 37 CFR § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The undersigned, Professor Dr. Florian Holsboer, declares the following:

1. I received my Ph.D. degree in Physical Chemistry from the Ludwig Maximilians University of Munich, Germany, in 1975, and my MD. degree from the Ludwig Maximilians University of Munich, Germany, in 1979. I have been working in the field of psychiatry since 1979. A copy of my resume is attached as Exhibit A1.

2. Currently I am the Director of the Max Planck Institute of Psychiatry, located in Munich, Germany. I have published more than 750 scientific articles in the field of psychiatry. I am also a respected member of numerous scientific organizations, including the American College of Psychiatrists (USA), the American College of Neuropsychopharmacology (USA), the Society of Biological Psychiatry (USA), and the Federation of European Neuroscience.

3. I received many distinguished awards, including the Freedom to Discover Unrestricted Neuroscience Research Grant of the Bristol-Myers Squibb Foundation (2004), the ECNP Neuropsychopharmacology Award (2006), and Doctor Honoris Causas from the University of Leiden (2008).

4. I understand that the U.S. Patent and Trademark Office has cited U.S. Patent No. 6,323,236 B2 to McElroy against the claimed invention of the present application in the Office Actions dated January 7, 2008, and July 11, 2008. I have read the Office Actions in this application and the cited reference. In this regard, I understand that the U.S. Patent and Trademark Office's position is that McElroy anticipates the claimed invention, because the references teaches a method comprising the administration of tenidap for the treatment of Impulse Control Disorders (ICDs) and reports the hypothesis that ICDs may be related to mood disorder or may be forms of affective spectrum disorder, a hypothesized family of disorders that share at least one common physiologic abnormality with major depression.

5. I submit this declaration to establish that affective disorders, including depression, anxiety, unipolar disorder, bipolar disorders, mania, attention deficit hyperactive disorder (ADHD), substance abuse and other mood disorders, are different from Impulse Control Disorders (ICDs), as evidenced herein.

6. I assert that the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), published by the American Psychiatric Association, defines the various categories of mental disorders and provides diagnostic criteria for each mental disorder.

7. I state that the DSM-IV-TR classifies depression as a mood disorder and provides ICDs with their own classification, which is separate and distinct from mood disorders (*see* DSM-IV-TR attached herein as Exhibit B1, at page 20 for depressive disorders, and page 24 for Impulse Control Disorders). This distinction in the DSM-IV-TR clearly shows that ICDs and depression are separate and distinct disorders.

8. I state that ICDs include pathological gambling, kleptomania, intermittent explosive disorder, trichotillomania, pyromania, binge eating disorder, and impulse control disorders not otherwise specified, which may include compulsive internet use, compulsive sexual behaviour, and compulsive buying. The basic characteristics of ICDs are:

    - repetitive or compulsive engagement in a behaviour despite adverse consequences;
    - diminished control over the problematic behaviour;
    - an appetitive urge or craving state prior to engagement in the problematic behaviour; and
    - a hedonic quality during the performance of the problematic behaviour.

9. I assert that contrary to ICDs, depression is not associated with repetitive behaviours and is characterized by a combination of symptoms which include:

    - lowered mood;
    - loss of energy;
    - loss of libido;
    - loss of interest;
    - feeling of physical illness;
    - poor concentration;
    - altered appetite;
    - altered sleep, mostly decreased;
    - thoughts of death and suicide; and
    - a slowing down of physical and mental functions resulting in a relentless feeling of hopelessness, helplessness, guilt, and anxiety.

10. I declare that based on these characteristics, the person skilled in the art would unambiguously conclude that ICDs and depression are separate medical indications.

11. I assert that several studies investigating the use of different classes of psychotropic drugs including antidepressants, opioid antagonists, mood stabilizers and atypical antipsychotics as potential therapeutic option for ICDs did not show any difference between placebo group and groups treated with the antidepressants fluvoxamine or paroxetine (*see* Blanco *et al.*, 2002, *Ann Clin Psychiatry 14*: 9-15; and Ninan *et al.*, 2000, *J Clin Psychopharmacol 20*: 362–366; attached herein as Exhibit C1). For example, a 16-week, multi-centered, randomized, placebo-controlled, flexible-dosing, double-blind study assessing the efficacy of paroxetine in 76 patients suffering from pathological gambling showed no statistically improvement using paroxetine over placebo (*see* Grant *et al*,. 2003, *Int. Clin. Psychopharmacol. 18*:243–249, attached herein as Exhibit D1). These studies clearly establish that ICDs are distinct from depression.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

10-13-2008
Date

Prof. Dr. Florian Holsboer

EXHIBIT A1

Exhibit A1

CURRICULUM VITAE

Florian Holsboer, M.D., Ph.D.
Max Planck Institute of Psychiatry
D-80804 Munich
Germany
Tel. +49 / (0) 89 - 30 622-220
www.mpipsykl.mpg.de
www.holsboer.de

Current position
Director of the Max Planck Institute of Psychiatry, Munich - a research institute for disorders of the central nervous system, 120 research beds in 5 wards for psychiatry and neurology, 2 outpatient clinics. The Institute contains a broad basic science component ranging from molecular biology to pharmacology, human and mouse genetics, proteomics and chemical genomics. The research is conducted in altogether 28 research groups.

Studies

1965	Final examination at the Luitpold Gymnasium, Munich
1965 – 1971	Studies of chemistry , Ludwig Maximilians University Munich
1975	PhD thesis (physical chemistry): Neue chemische Anwendungen der Röntgenphotoelektronenspektroskopie
1974 – 1979	Studies of medicine ; Ludwig Maximilians University Munich
1979	MD thesis (biochemistry): Analyse der Steroidausscheidung im Harn mittels Glaskapillargaschromatographie und Massenspektroskopie – Ein Beitrag zur Methodik und Anwendung

Professional Experience

1979 – 1983	Residency at the Department of Psychiatry, University of Munich (Chairman: Prof. Dr. H. Hippius) and at the Department of Psychiatry, University of Mainz (Chairman: Prof. Dr. O. Benkert)
1984	Venia legendi for psychiatry (Habilitation)
1986	Nomination for Full Professorship of Clincial Neuroscience at the State University of New York at Buffalo, USA
1987	Nomination as Chair of the Department of Psychiatry, University of Zurich
1987 – 1989	Chairman Department of Psychiatry, University of Freiburg
since 1989	Director of the Max Planck Institute of Psychiatry, Munich
2003	Co-Founder of the Biotech Company Affectis Pharmaceuticals AG
2003 - 2007	Chairman of the Board of Directors, Affectis Pharmaceuticals AG
2007	Founder and Director of NeuroNova gGmbH

Main Focus of Research

- Central regulation of stress hormones and their relation to the pathogenesis of affective disorders
- Molecular and clinical psychopharmacology
- Development and analysis of mouse mutants
- Development of new drug treatments for depression, anxiety and insomnia
- Pharmacogenetics
- Biomarker development

Awards (selected)

1991	Honorary Professor of the Ludwig Maximilians University, Munich
1997	Gay Lussac/Alexander von Humboldt Award of the Ministry of Research, France
1998	Membership Leopoldina
1999	Honorary Member of the American College of Psychiatrists
2001	Spinoza Visiting Professorship of the Amsterdam University Society
2002	Marius-Tausk Visiting Professorship at the University of Leiden, The Netherlands
2002	Hans Selye Memorial Lectureship, Edinburgh, United Kingdom
2003	Anna Monica Prize, Germany
2004	Freedom to Discover Unrestricted Neuroscience Research Grant of the Bristol-Myers Squibb Foundation
2006	ECNP Neuropsychopharmacology Award 2006
2008	Doctor Honoris Causa from the University of Leiden, The Netherlands

Publications: over 750

Publications since 1993 (selected)

1. Spengler et al.: Differential signal transduction patternsof five splice variants of the PACAP receptor. *Nature* **365**: 170-175 (1993)
2. Rupprecht at al.: Progesterone receptor mediated effects of neuroactive steroids. *Neuron* **11**: 523-530 (1993)
3. Trapp et al.: Heterodimerization between mineralocorticoid and gluco-corticoid receptor: a new principle of glucocorticoid action in thecentral nervous system. *Neuron* **13**: 1-6 (1994)
4. Wiegers et al.: Glucocorticoids accelerate anti-T-cell receptor-induced T-cell growth. *Journal of Immunology* **155**: 1893-1902 (1995)
5. Lauer et al.: In quest of identifying vulnerability markers for psychiatric disorders by all-night polysomnography. *Archives of General Psychiatry* **52**: 145-153 (1995)
6. Linthorst et al.: Effect of bacterial endotoxin and interleukin-1ß on hippocampal serotonergic neurotransmission, behavioral activity, and free corticosterone levels: an in vivo microdialysis study. *Journal of Neuroscience* **15**:2920-2934 (1995)
7. Holsboer and Barden: Antidepressants and HPA regulation. *Endocrine Reviews* **17**: 187-205 (1996)
8. Patchev et al.: Neonatal treatment of rats with the neuroactive steroidtetra-hydrodeoxycorticosterone (THDOC) abolishes the behavioural and neuroendocrine consequences of adverse early life events. *The Journal of Clinical Investigations* **99**: 962-966 (1997)
9. Timpl et al.: Impaired stress responseand reduced anxiety in mice lacking a functional corticotropin-releasing hormone receptor 1. *Nature Genetics* **19**: 162-166 (1998)
10. Rupprecht and Holsboer: Neuroactive steroids: mechanisms of action and neuro-psychopharmacological perspectives. *Trends in Neuroscience* **22**: 410-416 (1999)
11. Behl and Holsboer: The female sex hormone estrogen as neuroprotectant: an actor on different stages. *Trends in Pharmacological Sciences*, **20**: 441-444 (1999)
12. Hrabé de Angelis et al.: Genome-wide, large-scale production of mutant mice by ENU mutagenesis. *Nature Genetics* **25**: 444-447 (2000)
13. Holsboer: The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology* **23**:477-501 (2000)
14. Holsboer: Antidepressant drug discovery in the postgenomic era. *World Journal of Biological Psychiatry* **2**:165-177 (2001)
15. Keck et al.: The anxiolytic effect of the CRH_1 receptor antagonist R121919 depends on innate emotionality in rats. *European Journal of Neuroscience* **13**:373-380 (2001)

16. Gesing et al.: Psychological stress increases hippocampal mineralocorticoid receptor levels: involvement of corticotropin-releasing hormone. *Journal of Neuroscience* **21**:4822-4829 (2001)
17. Sillaber et al.: Enhanced and delayed stress-induced alcohol drinking in mice lacking functional CRH1 receptors. *Science* **296**:931-933 (2002)
18. Keck et al.: Vasopressin mediates the response of the combined dexamethasone/CRH test in hyper-anxious rats: Implicationsfor pathogenesis of affective disorders. *Neuropsychopharmacology* **26**: 94-105 (2002)
19. Ströhle et al.: Induced panic attacks shift $GABA_A$ receptor modulatory neuroactive steroid composition in patients with panic disorder. *Archives of General Psychiatry* **60**: 161-168 (2003)
20. Páez-Pereda et al.: Involvement of bone morphogenetic protein 4 (BMP-4) in pituitary prolactinoma pathogenesis through a Smad/estrogen receptor crosstalk. *PNAS* **3**: 1034-1039 (2003)
21. Müller et al.: Limbic corticotropin-releasing hormone receptor 1 mediates anxiety-related behavior and hormonal adaptation to stress. *Nature Neuroscience* **6**: 1100-1107 (2003)
22. Oshima et al.: Altered serotonergic neurotransmission but normal hypothalamic-pituitary-adrenocortical axis activity in mice chronically treated with the corticotropin-releasing hormone receptor type 1 antagonist NBI 30775. *Neuropsychopharmacology* **28**: 2148-2159 (2003)
23. Schmidt et al.: Essential role of the unusual DNA-binding motif of BAG-1 for inhibition of the glucocorticoid receptor. *Journal of Biological Chemistry* **278**: 4926-4931 (2003)
24. Holsboer: CRH-modulators and depression. *Current Opinion in Investigational Drugs* **4**: 46-50 (2003)
25. Uhr et al.: Differential enhancement of antidepressant penetration into the brain in mice with abcb1ab (mdr1ab) P-glycoprotein gene disruption. *Biological Psychiatry* **54**: 840-846 (2003)
26. Murgatroyd et al.: Impaired repression at a vasopressin promoter polymorphism underlies overexpression of vasopressin in a rat model of trait anxiety. *Journal of Neuroscience* **24**: 7762-7770 (2004)
27. Binder et al.: Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nature Genetics* **36**: 1319-1325 (2004)
28. Vila et al.: Sonic hedgehog regulates CRH signal transduction in the adult pituitary. *FASEB* **19**: 281-283 (2005)
29. De Kloet et al: Stress and the brain: from adaptation to disease. *Nature Reviews Neuroscience* **6**: 463-475 (2005)
30. Rüegg et al.: Cofilin 1 is revealed as inhibitor of glucocorticoid receptor by creation and analysis of hormone-resistant cells. *Molecular and Cellular Biology* **24**: 9371-9382 (2004)
31. Refojo et al: CRH activates ERK1/2 MAPK in specific brain areas. *PNAS* **102**: 6183-6188 (2005)
32. Wochnik et al.: FK506-binding proteins 51 and 52 differentially regulate dynein interaction and nuclear translocation of the glucocorticoid receptor in mammalian cells. *Journal of Biological Chemistry* **280**: 4609-4616 (2005)
33. Müller and Holsboer: Mice with mutations in the HPA-system as models for symptoms of depression. *Biological Psychiatry* **59**: 1104-1115 (2006)
34. Binder and Holsboer: Pharmacogenomics and antidepressant drugs. *Annals of Medicine* **38**: 82-94 (2006)
35. Lucae et al: *P2RX7*, a gene coding for a purinergic ligand-gated ion channel, is associated with major depressive disorder. *Human Molecular Genetics* **15**: 2438-2445 (2006)
36. Arzt and Holsboer: CRF signaling: molecular specificity for drug targeting in the CNS. *Trends in Pharmacological Sciences* **27**: 531-538 (2006)

37. Barden et al.: Analysis of single nucleotide polymorphisms in genes in the chromosome 12Q24.31 region points to P2RX7 as a susceptibility gene to bipolar affective disorder. *American Journal of Medical Genetics* **141B:** 374-382 (2006)
38. Winkelmann et al: Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. *Nature Genetics* **39:** 1000-1006 (2007)
39. Carbia-Nagashima et al: RSUME, a small RWD-containing protein, enhances SUMO conjugation and stabilizes HIF-1alpha during hypoxia. *Cell* **131:** 309-323 (2007)
40. Uhr et al: Polymorphisms in the drug-transporter gene ABCB1 predict antidepressant treatment response in depression. *Neuron* **57:** 203-209 (2008)

Editor-in-Chief Journal of Psychiatric Research

Committees (selected)

1990 - 1999	Chairman of the Founding Committee and of the Scientific Advisory Board of the Research Institute for Molecular Pharmacology (FMP), Berlin-Buch
1990 – 1996 and 2000 - 2003	Member of the *Gesundheitsforschungsrat* (Health Research Council) of the Federal Ministry for Education, Sciene, Investigation and Technology
1993 - 2000	Member of the Scientific Committee of the *Gesundheitsforschungsrat* (Health Research Council) of the Federal Ministry for Education, Science, Investigation and Technology
2003 -	Medication Development Task Force of the ACNP

Memberships of Scientific Associations (selected)

- American College of Neuropsychopharmacology (ACNP), Foreign Corresponding Member
- American College of Psychiatrists (Honorary Member)
- Society of Biological Psychiatry (USA)
- Society of Neuroscience (USA)
- Federation of European Neuroscience (FENS)
- Arbeitsgemeinschaft für Neuropharmakologie und Psychopharmakologie AGNP (President: 2000-2003)

Munich, February 2008

Florian Holsboer

EXHIBIT B1

Exhibit 31

DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS

FOURTH EDITION

TEXT REVISION

DSM-IV-TR®

Published by the
American Psychiatric Association
Arlington, VA

Manufactured in the United States of America on acid-free paper.

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American Psychiatric Association
1000 Wilson Boulevard
Arlington, VA 22209-3901
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Library of Congress Cataloging-in-Publication Data
Diagnostic and statistical manual of mental disorders : DSM-IV.—4th ed., text revision.
p. ; cm.
Prepared by the Task Force on DSM-IV and other committees and work groups of the American Psychiatric Association.
Includes index.
ISBN 0-89042-024-6 (casebound : alk. paper)—ISBN 0-89042-025-4 (pbk. : alk. paper)
1. Mental Illness—Classification—Handbooks, manuals, etc. 2. Mental Illness—Diagnosis—Handbooks, manuals, etc. I. Title: DSM-IV. II. American Psychiatric Association. III. American Psychiatric Association. Task Force on DSM-IV.
[DNLM: 1. Mental Disorders—classification. 2. Mental Disorders—diagnosis.
WM 15 D536 2000]
RC455.2.C4 D536 2000
616.89'075—dc21

00-024852

British Library Cataloguing in Publication Data
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Text Design—Anne Barnes
Manufacturing—R. R. Donnelley & Sons Company

Use of the Manual

linth Revision, Clinical
e official coding system
l Health Problems, Tenth
ally, this appendix con-
stic codes.

ary of Culture-Bound
e first provides an out-
n systematically evalu-
context. The second is

names of the advisers
ations that contributed

ndix lists the names of

DSM-IV-TR Classification

NOS = Not Otherwise Specified.

An *x* appearing in a diagnostic code indicates that a specific code number is required.

An ellipsis (. . .) is used in the names of certain disorders to indicate that the name of a specific mental disorder or general medical condition should be inserted when recording the name (e.g., 293.0 Delirium Due to Hypothyroidism).

Numbers in parentheses are page numbers.

If criteria are currently met, one of the following severity specifiers may be noted after the diagnosis:

Mild
Moderate
Severe

If criteria are no longer met, one of the following specifiers may be noted:

In Partial Remission
In Full Remission
Prior History

Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence (39)

Delirium, Dementia, and Amnestic and Other Cognitive Disorders (135)

SORDERS (116)
(116)
nstipation and
w Incontinence
Constipation and
w Incontinence
Not Due to a General
ndition) (118)
cturnal Only/Diurnal
nal and Diurnal

RS OF INFANCY, ADOLESCENCE

Anxiety Disorder

ly Onset
Autism (125)
Attachment Disorder
or Early Childhood

nhibited Type/
Type
e Movement Disorder

h Self-Injurious Behavior
f Infancy, Childhood,
ence NOS (134)

ientia, and Other Cognitive

Due to . . . *[Indicate the Medical Condition]* (141)
Intoxication Delirium
bstance-Related
or substance-specific
)
Withdrawal
(refer to Substance-Disorders for substance-specific) (143)

—.— Delirium Due to Multiple Etiologies *(code each of the specific etiologies)* (146)
780.09 Delirium NOS (147)

DEMENTIA (147)
294.xx Dementia of the Alzheimer's Type, With Early Onset *(also code 331.0 Alzheimer's disease on Axis III)* (154)
.10 Without Behavioral Disturbance
.11 With Behavioral Disturbance
294.xx Dementia of the Alzheimer's Type, With Late Onset *(also code 331.0 Alzheimer's disease on Axis III)* (154)
.10 Without Behavioral Disturbance
.11 With Behavioral Disturbance
290.xx Vascular Dementia (158)
.40 Uncomplicated
.41 With Delirium
.42 With Delusions
.43 With Depressed Mood
Specify if: With Behavioral Disturbance

Code presence or absence of a behavioral disturbance in the fifth digit for Dementia Due to a General Medical Condition:
0 = Without Behavioral Disturbance
1 = With Behavioral Disturbance

294.1x Dementia Due to HIV Disease *(also code 042 HIV on Axis III)* (163)
294.1x Dementia Due to Head Trauma *(also code 854.00 head injury on Axis III)* (164)
294.1x Dementia Due to Parkinson's Disease *(also code 332.82 Dementia with Lewy bodies on Axis III)* (164)
294.1x Dementia Due to Huntington's Disease *(also code 333.4 Huntington's disease on Axis III)* (165)
294.1x Dementia Due to Pick's Disease *(also code 331.11 Pick's disease on Axis III)* (165)
294.1x Dementia Due to Creutzfeldt-Jakob Disease *(also code 046.1 Creutzfeldt-Jakob disease on Axis III)* (166)
294.1x Dementia Due to . . . *[Indicate the General Medical Condition not listed above] (also code the general medical condition on Axis III)* (167)
—.— Substance-Induced Persisting Dementia *(refer to Substance-Related Disorders for substance-specific codes)* (168)
—.— Dementia Due to Multiple Etiologies *(code each of the specific etiologies)* (170)
294.8 Dementia NOS (171)

AMNESTIC DISORDERS (172)
294.0 Amnestic Disorder Due to . . . *[Indicate the General Medical Condition]* (175)
Specify if: Transient/Chronic
—.— Substance-Induced Persisting Amnestic Disorder *(refer to Substance-Related Disorders for substance-specific codes)* (177)
294.8 Amnestic Disorder NOS (179)

OTHER COGNITIVE DISORDERS (179)
294.9 Cognitive Disorder NOS (179)

Mental Disorders Due to a General Medical Condition Not Elsewhere Classified (181)

293.89 Catatonic Disorder Due to . . . *[Indicate the General Medical Condition]* (185)
310.1 Personality Change Due to . . . *[Indicate the General Medical Condition]* (187)

Specify type: Labile Type/Disinhibited Type/Aggressive Type/Apathetic Type/Paranoid Type/Other Type/Combined Type/Unspecified Type

293.9 Mental Disorder NOS
Due to . . . *[Indicate the General Medical Condition]* (190)

Substance-Related Disorders (191)

The following specifiers apply to Substance Dependence as noted:

[a]With Physiological Dependence/Without Physiological Dependence

[b]Early Full Remission/Early Partial Remission/Sustained Full Remission/Sustained Partial Remission

[c]In a Controlled Environment

[d]On Agonist Therapy

The following specifiers apply to Substance-Induced Disorders as noted:

[I]With Onset During Intoxication/[W]With Onset During Withdrawal

ALCOHOL-RELATED DISORDERS (212)

Alcohol Use Disorders (213)

303.90 Alcohol Dependence[a,b,c] (213)
305.00 Alcohol Abuse (214)

Alcohol-Induced Disorders (214)

303.00 Alcohol Intoxication (214)
291.81 Alcohol Withdrawal (215)
Specify if: With Perceptual Disturbances
291.0 Alcohol Intoxication Delirium (143)
291.0 Alcohol Withdrawal Delirium (143)
291.2 Alcohol-Induced Persisting Dementia (168)
291.1 Alcohol-Induced Persisting Amnestic Disorder (177)
291.x Alcohol-Induced Psychotic Disorder (398)
.5 With Delusions[I,W]
.3 With Hallucinations[I,W]
291.89 Alcohol-Induced Mood Disorder[I,W] (405)
291.89 Alcohol-Induced Anxiety Disorder[I,W] (479)
291.89 Alcohol-Induced Sexual Dysfunction[I] (562)
291.82 Alcohol-Induced Sleep Disorder[I,W] (655)
291.9 Alcohol-Related Disorder NOS (223)

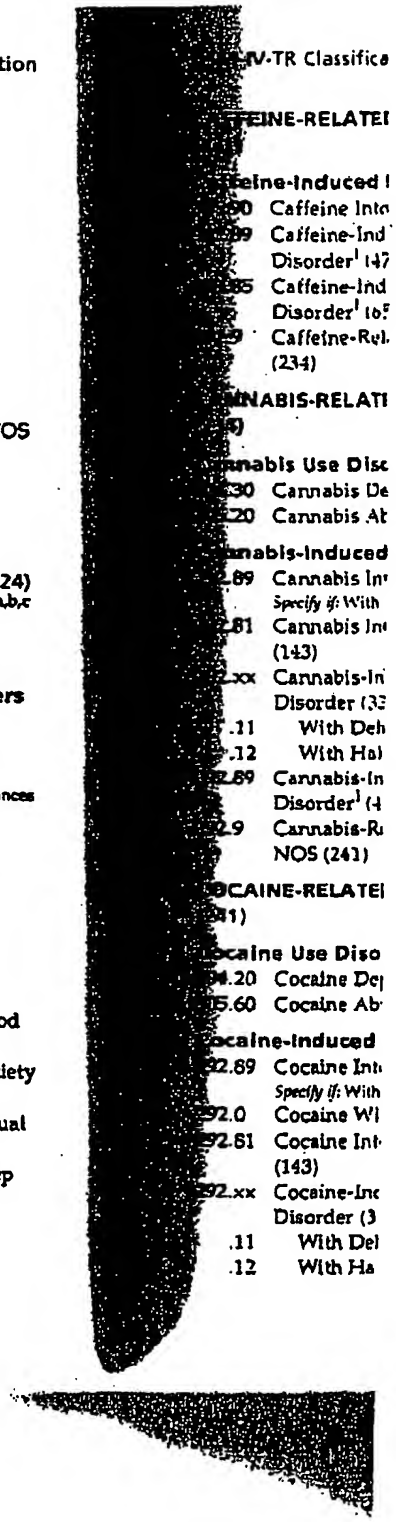
AMPHETAMINE (OR AMPHETAMINE-LIKE)–RELATED DISORDERS (223)

Amphetamine Use Disorders (224)

304.40 Amphetamine Dependence[a,b,c] (224)
305.70 Amphetamine Abuse (225)

Amphetamine-Induced Disorders (226)

292.89 Amphetamine Intoxication (226)
Specify if: With Perceptual Disturbances
292.0 Amphetamine Withdrawal (227)
292.81 Amphetamine Intoxication Delirium (143)
292.xx Amphetamine-Induced Psychotic Disorder (338)
.11 With Delusions[I]
.12 With Hallucinations[I]
292.84 Amphetamine-Induced Mood Disorder[I,W] (405)
292.89 Amphetamine-Induced Anxiety Disorder[I] (479)
292.89 Amphetamine-Induced Sexual Dysfunction[I] (562)
292.85 Amphetamine-Induced Sleep Disorder[I,W] (655)
292.9 Amphetamine-Related Disorder NOS (231)



CAFFEINE-RELATED DISORDERS (231)

Caffeine-Induced Disorders (232)
305.90 Caffeine Intoxication (232)
292.89 Caffeine-Induced Anxiety Disorder[I] (479)
292.85 Caffeine-Induced Sleep Disorder[I] (655)
292.9 Caffeine-Related Disorder NOS (234)

CANNABIS-RELATED DISORDERS (234)

Cannabis Use Disorders (236)
304.30 Cannabis Dependence[a,b,c] (236)
305.20 Cannabis Abuse (236)

Cannabis-Induced Disorders (237)
292.89 Cannabis Intoxication (237)
Specify if: With Perceptual Disturbances
292.81 Cannabis Intoxication Delirium (143)
292.xx Cannabis-Induced Psychotic Disorder (338)
.11 With Delusions[I]
.12 With Hallucinations[I]
292.89 Cannabis-Induced Anxiety Disorder[I] (479)
292.9 Cannabis-Related Disorder NOS (241)

COCAINE-RELATED DISORDERS (241)

Cocaine Use Disorders (242)
304.20 Cocaine Dependence[a,b,c] (242)
305.60 Cocaine Abuse (243)

Cocaine-Induced Disorders (244)
292.89 Cocaine Intoxication (244)
Specify if: With Perceptual Disturbances
292.0 Cocaine Withdrawal (245)
292.81 Cocaine Intoxication Delirium (143)
292.xx Cocaine-Induced Psychotic Disorder (338)
.11 With Delusions[I]
.12 With Hallucinations[I]
292.84 Cocaine-Induced Mood Disorder[I,W] (405)
292.89 Cocaine-Induced Anxiety Disorder[I,W] (479)
292.89 Cocaine-Induced Sexual Dysfunction[I] (562)
292.85 Cocaine-Induced Sleep Disorder[I,W] (655)
292.9 Cocaine-Related Disorder NOS (250)

HALLUCINOGEN-RELATED DISORDERS (250)

Hallucinogen Use Disorders (251)
304.50 Hallucinogen Dependence[b,c] (251)
305.30 Hallucinogen Abuse (252)

Hallucinogen-Induced Disorders (252)
292.89 Hallucinogen Intoxication (252)
292.89 Hallucinogen Persisting Perception Disorder (Flashbacks) (253)
292.81 Hallucinogen Intoxication Delirium (143)
292.xx Hallucinogen-Induced Psychotic Disorder (338)
.11 With Delusions[I]
.12 With Hallucinations[I]
292.84 Hallucinogen-Induced Mood Disorder[I] (405)
292.89 Hallucinogen-Induced Anxiety Disorder[I] (479)
292.9 Hallucinogen-Related Disorder NOS (256)

INHALANT-RELATED DISORDERS (257)

Inhalant Use Disorders (258)
304.60 Inhalant Dependence[b,c] (258)
305.90 Inhalant Abuse (259)

Inhalant-Induced Disorders (259)
292.89 Inhalant Intoxication (259)
292.81 Inhalant Intoxication Delirium (143)

292.82 Inhalant-Induced Persisting Dementia (168)
292.xx Inhalant-Induced Psychotic Disorder (338)
.11 With Delusions[I]
.12 With Hallucinations[I]
292.84 Inhalant-Induced Mood Disorder[I] (405)
292.89 Inhalant-Induced Anxiety Disorder[I] (479)
292.9 Inhalant-Related Disorder NOS (263)

NICOTINE-RELATED DISORDERS (264)

Nicotine Use Disorder (264)
305.1 Nicotine Dependence[a,b] (264)

Nicotine-Induced Disorder (265)
292.0 Nicotine Withdrawal (265)
292.9 Nicotine-Related Disorder NOS (269)

OPIOID-RELATED DISORDERS (269)

Opioid Use Disorders (270)
304.00 Opioid Dependence[a,b,c,d] (270)
305.50 Opioid Abuse (271)

Opioid-Induced Disorders (271)
292.89 Opioid Intoxication (271)
Specify if: With Perceptual Disturbances
292.0 Opioid Withdrawal (272)
292.81 Opioid Intoxication Delirium (143)
292.xx Opioid-Induced Psychotic Disorder (338)
.11 With Delusions[I]
.12 With Hallucinations[I]
292.84 Opioid-Induced Mood Disorder[I] (405)
292.89 Opioid-Induced Sexual Dysfunction[I] (562)
292.85 Opioid-Induced Sleep Disorder[I,W] (655)
292.9 Opioid-Related Disorder NOS (277)

PHENCYCLIDINE (OR PHENCYCLIDINE-LIKE)–RELATED DISORDERS (278)

Phencyclidine Use Disorders (279)
304.60 Phencyclidine Dependence[b,c] (279)
305.90 Phencyclidine Abuse (279)

Phencyclidine-Induced Disorders (280)
292.89 Phencyclidine Intoxication (280)
Specify if: With Perceptual Disturbances
292.81 Phencyclidine Intoxication Delirium (143)
292.xx Phencyclidine-Induced Psychotic Disorder (338)
.11 With Delusions[I]
.12 With Hallucinations[I]
292.84 Phencyclidine-Induced Mood Disorder[I] (405)
292.89 Phencyclidine-Induced Anxiety Disorder[I] (479)
292.9 Phencyclidine-Related Disorder NOS (283)

SEDATIVE-, HYPNOTIC-, OR ANXIOLYTIC-RELATED DISORDERS (284)

Sedative, Hypnotic, or Anxiolytic Use Disorders (285)
304.10 Sedative, Hypnotic, or Anxiolytic Dependence[a,b,c] (285)
305.40 Sedative, Hypnotic, or Anxiolytic Abuse (286)

Sedative-, Hypnotic-, or Anxiolytic-Induced Disorders (286)
292.89 Sedative, Hypnotic, or Anxiolytic Intoxication (286)
292.0 Sedative, Hypnotic, or Anxiolytic Withdrawal (287)
Specify if: With Perceptual Disturbances
292.81 Sedative, Hypnotic, or Anxiolytic Intoxication Delirium (143)
292.81 Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium (143)

OR
IKE)–RELATED

Disorders (279)
ne Dependence[b,c]

ne Abuse (279)
luced Disorders

ne Intoxication (280)
Perceptual Disturbances
ne Intoxication
43)
ne-Induced
isorder (338)
usions[I]
lucinations[I]
ne-Induced Mood
405)
ne-Induced Anxiety
479)
ne-Related Disorder

IOTIC-, OR
ATED DISORDERS

tic or Anxiolytic
35)
lypnotic, or
Dependence[a,b,c]

lypnotic, or
Abuse (286)
otic-, or
ed Disorders (286)
lypnotic, or
Intoxication (286)
lypnotic, or
Withdrawal (287)
h Perceptual Disturbances
Hypnotic, or
Intoxication
143)
Hypnotic, or
Withdrawal
143)

292.82 Sedative-, Hypnotic-, or Anxiolytic-Induced Persisting Dementia (168)
292.83 Sedative-, Hypnotic-, or Anxiolytic-Induced Persisting Amnestic Disorder (177)
292.xx Sedative-, Hypnotic-, or Anxiolytic-Induced Psychotic Disorder (338)
.11 With Delusions[I,W]
.12 With Hallucinations[I,W]
292.84 Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder[I,W] (405)
292.89 Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorder[W] (479)
292.89 Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction[I] (562)
292.85 Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep Disorder[I,W] (655)
292.9 Sedative-, Hypnotic-, or Anxiolytic-Related Disorder NOS (293)

POLYSUBSTANCE-RELATED DISORDER (293)
304.80 Polysubstance Dependence[a,b,c,d] (253)

OTHER (OR UNKNOWN) SUBSTANCE–RELATED DISORDERS (294)

Other (or Unknown) Substance Use Disorders (295)
304.90 Other (or Unknown) Substance Dependence[a,b,c,d] (192)
305.90 Other (or Unknown) Substance Abuse (198)

Other (or Unknown) Substance–Induced Disorders (295)
292.89 Other (or Unknown) Substance Intoxication (199)
Specify if: With Perceptual Disturbances
292.0 Other (or Unknown) Substance Withdrawal (201)
Specify if: With Perceptual Disturbances
292.81 Other (or Unknown) Substance–Induced Delirium (143)
292.82 Other (or Unknown) Substance–Induced Persisting Dementia (168)
292.83 Other (or Unknown) Substance–Induced Persisting Amnestic Disorder (177)
292.xx Other (or Unknown) Substance–Induced Psychotic Disorder (338)
.11 With Delusions[I,W]
.12 With Hallucinations[I,W]
292.84 Other (or Unknown) Substance–Induced Mood Disorder[I,W] (405)
292.89 Other (or Unknown) Substance–Induced Anxiety Disorder[I,W] (479)
292.89 Other (or Unknown) Substance–Induced Sexual Dysfunction[I] (562)
292.85 Other (or Unknown) Substance–Induced Sleep Disorder[I,W] (655)
292.9 Other (or Unknown) Substance–Related Disorder NOS (295)

Schizophrenia and Other Psychotic Disorders (297)

295.xx Schizophrenia (298)
The following Classification of Longitudinal Course applies to all subtypes of Schizophrenia:

Episodic With Interepisode Residual Symptoms (*specify if:* With Prominent Negative Symptoms)/Episodic With No Interepisode Residual Symptoms

Continuous (*specify if*: With Prominent Negative Symptoms)
Single Episode In Partial Remission (*specify if*: With Prominent Negative Symptoms)/ Single Episode In Full Remission
Other or Unspecified Pattern

.30 Paranoid Type (313)
.10 Disorganized Type (314)
.20 Catatonic Type (315)
.90 Undifferentiated Type (316)
.60 Residual Type (316)

295.40 Schizophreniform Disorder (317)
Specify if: Without Good Prognostic Features/With Good Prognostic Features

295.70 Schizoaffective Disorder (319)
Specify type: Bipolar Type/Depressive Type

297.1 Delusional Disorder (323)
Specify type: Erotomanic Type/ Grandiose Type/Jealous Type/ Persecutory Type/Somatic Type/ Mixed Type/Unspecified Type

298.8 Brief Psychotic Disorder (329)
Specify if: With Marked Stressor(s)/ Without Marked Stressor(s)/With Postpartum Onset

297.3 Shared Psychotic Disorder (332)

293.xx Psychotic Disorder Due to . . . *[Indicate the General Medical Condition]* (334)
.81 With Delusions
.82 With Hallucinations

——.— Substance-Induced Psychotic Disorder *(refer to Substance-Related Disorders for substance-specific codes)* (338)
Specify if: With Onset During Intoxication/With Onset During Withdrawal

298.9 Psychotic Disorder NOS (343)

Mood Disorders (345)

Code current state of Major Depressive Disorder or Bipolar I Disorder in fifth digit:

1 = Mild
2 = Moderate
3 = Severe Without Psychotic Features
4 = Severe With Psychotic Features
Specify: Mood-Congruent Psychotic Features/Mood-Incongruent Psychotic Features
5 = In Partial Remission
6 = In Full Remission
0 = Unspecified

The following specifiers apply (for current or most recent episode) to Mood Disorders as noted:

[a]Severity/Psychotic/Remission Specifiers/ [b]Chronic/[c]With Catatonic Features/[d]With Melancholic Features/[e]With Atypical Features/[f]With Postpartum Onset

The following specifiers apply to Mood Disorders as noted:

[g]With or Without Full Interepisode Recovery/ [h]With Seasonal Pattern/[i]With Rapid Cycling

DEPRESSIVE DISORDERS (369)

296.xx Major Depressive Disorder (369)
.2x Single Episode[a,b,c,d,e,f]
.3x Recurrent[a,b,c,d,e,f,g,h]

300.4 Dysthymic Disorder (376)
Specify if: Early Onset/Late Onset
Specify: With Atypical Features

311 Depressive Disorder NOS (381)

BIPOLAR DISORDERS (382)

296.xx Bipolar I Disorder (382)
.0x Single Manic Episode[a,c,f]
Specify if: Mixed
.40 Most Recent Episode Hypomanic[g,h,i]
.4x Most Recent Episode Manic[a,c,f,g,h,i]

.6x Most Recen
Mixed[a,c,f,g
.5x Most Recer
Depressed[a
.7 Most Recer
Unspecifie
296.89 Bipolar II Dis
(392)
Specify (current
Hypomanic/De
301.13 Cyclothymic
296.80 Bipolar Disor
293.83 Mood Disorc
[Indicate the C
Condition] (4
Specify type: Wi
With Major De
With Manic Fe
Features
——.— Substance-I
Disorder (re
Related Disc
specific code
Specify type: W
With Manic F
Features
Specify if: Wit
Intoxication/
Withdrawal
296.90 Mood Disc

Anxiety Disorc

300.01 Panic Dis
Agoraphc
300.21 Panic Dis
Agoraphi
300.22 Agoraphi
of Panic I
300.29 Specific I
Specify type
Environme
Injury Typ
Type
300.23 Social Ph
Specify if: C

's (345)

Major Depressive Disorder in fifth digit:

Psychotic Features
chotic Features
-Congruent Psychotic
d-Incongruent Psychotic

rs apply (for current or t Mood Disorders as

Remission Specifiers/ Catatonic Features/[d]With ure/[e]With Atypical Postpartum Onset

ers apply to Mood

ll Interepisode Recovery/ Pattern/[i]With Rapid

ORDERS (369)
ressive Disorder

Episode[a,b,c,d,e,f]
nt[a,b,c,d,e,f,g,h]
Disorder (376)
y Onset/Late Onset
Atypical Features
e Disorder NOS (381)

DERS (382)
Disorder (382)
Manic Episode[a,c,f]
ed
ecent Episode
anic[g,h,i]
ecent Episode
c,f,g,h,i]

.6x Most Recent Episode Mixed[a,c,f,g,h,i]
.5x Most Recent Episode Depressed[a,b,c,d,e,f,g,h]
.7 Most Recent Episode Unspecified[g,h,i]

296.89 Bipolar II Disorder[a,b,c,d,e,f,g,h,i] (392)
Specify (current or most recent episode): Hypomanic/Depressed

301.13 Cyclothymic Disorder (398)

296.80 Bipolar Disorder NOS (400)

293.83 Mood Disorder Due to . . . *[Indicate the General Medical Condition]* (401)
Specify type: With Depressive Features/ With Major Depressive-Like Episode/ With Manic Features/With Mixed Features

—.— Substance-Induced Mood Disorder *(refer to Substance-Related Disorders for substance-specific codes)* (405)
Specify type: With Depressive Features/ With Manic Features/With Mixed Features
Specify if: With Onset During Intoxication/With Onset During Withdrawal

296.90 Mood Disorder NOS (410)

Anxiety Disorders (429)

300.01 Panic Disorder Without Agoraphobia (433)

300.21 Panic Disorder With Agoraphobia (433)

300.22 Agoraphobia Without History of Panic Disorder (441)

300.29 Specific Phobia (443)
Specify type: Animal Type/Natural Environment Type/Blood-Injection-Injury Type/Situational Type/Other Type

300.23 Social Phobia (450)
Specify if: Generalized

300.3 Obsessive-Compulsive Disorder (456)
Specify if: With Poor Insight

309.81 Posttraumatic Stress Disorder (463)
Specify if: Acute/Chronic
Specify if: With Delayed Onset

308.3 Acute Stress Disorder (469)

300.02 Generalized Anxiety Disorder (472)

293.84 Anxiety Disorder Due to . . . *[Indicate the General Medical Condition]* (476)
Specify if: With Generalized Anxiety/ With Panic Attacks/With Obsessive-Compulsive Symptoms

—.— Substance-Induced Anxiety Disorder *(refer to Substance-Related Disorders for substance-specific codes)* (479)
Specify if: With Generalized Anxiety/ With Panic Attacks/With Obsessive-Compulsive Symptoms/With Phobic Symptoms
Specify if: With Onset During Intoxication/With Onset During Withdrawal

300.00 Anxiety Disorder NOS (484)

Somatoform Disorders (485)

300.81 Somatization Disorder (486)

300.82 Undifferentiated Somatoform Disorder (490)

300.11 Conversion Disorder (492)
Specify type: With Motor Symptom or Deficit/With Sensory Symptom or Deficit/With Seizures or Convulsions/ With Mixed Presentation

307.xx Pain Disorder (498)
.80 Associated With Psychological Factors
.89 Associated With Both Psychological Factors and a General Medical Condition
Specify if: Acute/Chronic

300.7 Hypochondriasis (504)
Specify if: With Poor Insight
300.7 Body Dysmorphic Disorder (507)
300.82 Somatoform Disorder NOS (511)

Factitious Disorders (513)

300.xx Factitious Disorder (513)
.16 With Predominantly Psychological Signs and Symptoms
.19 With Predominantly Physical Signs and Symptoms
.19 With Combined Psychological and Physical Signs and Symptoms
300.19 Factitious Disorder NOS (517)

Dissociative Disorders (519)

300.12 Dissociative Amnesia (520)
300.13 Dissociative Fugue (523)
300.14 Dissociative Identity Disorder (526)
300.6 Depersonalization Disorder (530)
300.15 Dissociative Disorder NOS (532)

Sexual and Gender Identity Disorders (535)

SEXUAL DYSFUNCTIONS (535)

The following specifiers apply to all primary Sexual Dysfunctions:

Lifelong Type/Acquired Type

Generalized Type/Situational Type

Due to Psychological Factors/Due to Combined Factors

Sexual Desire Disorders (539)

302.71 Hypoactive Sexual Desire Disorder (539)
302.79 Sexual Aversion Disorder (541)

Sexual Arousal Disorders (543)

302.72 Female Sexual Arousal Disorder (543)
302.72 Male Erectile Disorder (545)

Orgasmic Disorders (547)

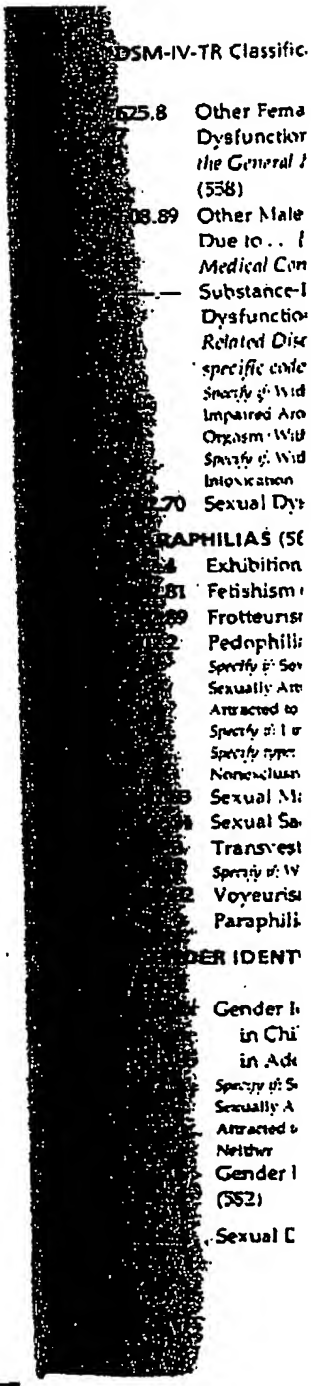
302.73 Female Orgasmic Disorder (547)
302.74 Male Orgasmic Disorder (550)
302.75 Premature Ejaculation (552)

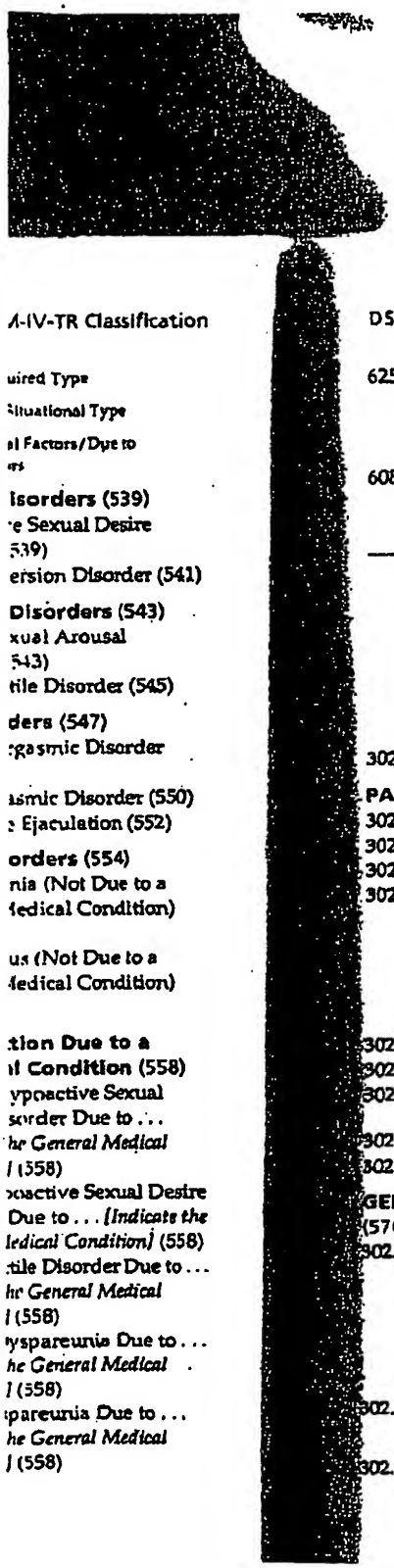
Sexual Pain Disorders (554)

302.76 Dyspareunia (Not Due to a General Medical Condition) (554)
306.51 Vaginismus (Not Due to a General Medical Condition) (556)

Sexual Dysfunction Due to a General Medical Condition (558)

625.8 Female Hypoactive Sexual Desire Disorder Due to . . . *[Indicate the General Medical Condition]* (558)
608.89 Male Hypoactive Sexual Desire Disorder Due to . . . *[Indicate the General Medical Condition]* (558)
607.84 Male Erectile Disorder Due to . . . *[Indicate the General Medical Condition]* (558)
625.0 Female Dyspareunia Due to . . . *[Indicate the General Medical Condition]* (558)
608.89 Male Dyspareunia Due to . . . *[Indicate the General Medical Condition]* (558)





uired Type
Situational Type
al Factors/Due to
ers

Disorders (539)
e Sexual Desire
539)
ersion Disorder (541)

Disorders (543)
xual Arousal
543)
tile Disorder (545)

ders (547)
gasmic Disorder

asmic Disorder (550)
Ejaculation (552)

orders (554)
nia (Not Due to a
Medical Condition)

us (Not Due to a
Medical Condition)

tion Due to a
al Condition (558)
ypoactive Sexual
sorder Due to . . .
he General Medical
l (558)
oactive Sexual Desire
Due to . . . *[Indicate the*
Medical Condition] (558)
tile Disorder Due to . . .
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yspareunia Due to . . .
he General Medical
l (558)
pareunia Due to . . .
he General Medical
l (558)

625.8 Other Female Sexual Dysfunction Due to . . . *[Indicate the General Medical Condition]* (558)
608.89 Other Male Sexual Dysfunction Due to . . . *[Indicate the General Medical Condition]* (558)
—.— Substance-Induced Sexual Dysfunction *(refer to Substance-Related Disorders for substance-specific codes)* (562)
Specify if: With Impaired Desire/With Impaired Arousal/With Impaired Orgasm/With Sexual Pain
Specify if: With Onset During Intoxication
302.70 Sexual Dysfunction NOS (565)

PARAPHILIAS (566)
302.4 Exhibitionism (569)
302.81 Fetishism (569)
302.89 Frotteurism (570)
302.2 Pedophilia (571)
Specify if: Sexually Attracted to Males/Sexually Attracted to Females/Sexually Attracted to Both
Specify if: Limited to Incest
Specify type: Exclusive Type/Nonexclusive Type
302.83 Sexual Masochism (572)
302.84 Sexual Sadism (573)
302.3 Transvestic Fetishism (574)
Specify if: With Gender Dysphoria
302.82 Voyeurism (575)
302.9 Paraphilia NOS (576)

GENDER IDENTITY DISORDERS (576)
302.xx Gender Identity Disorder (576)
.6 in Children
.85 in Adolescents or Adults
Specify if: Sexually Attracted to Males/Sexually Attracted to Females/Sexually Attracted to Both/Sexually Attracted to Neither
302.6 Gender Identity Disorder NOS (582)

302.9 Sexual Disorder NOS (582)

Eating Disorders (583)

307.1 Anorexia Nervosa (583)
Specify type: Restricting Type; Binge-Eating/Purging Type
307.51 Bulimia Nervosa (589)
Specify type: Purging Type/Nonpurging Type
307.50 Eating Disorder NOS (594)

Sleep Disorders (597)

PRIMARY SLEEP DISORDERS (598)

Dyssomnias (598)
307.42 Primary Insomnia (599)
307.44 Primary Hypersomnia (604)
Specify if: Recurrent
347.00 Narcolepsy (609)
780.57 Breathing-Related Sleep Disorder (615)
327.3x Circadian Rhythm Sleep Disorder (622)
.31 Delayed Sleep Phase Type
.35 Jet Lag Type
.36 Shift Work Type
.30 Unspecified Type
307.47 Dyssomnia NOS (629)

Parasomnias (630)
307.47 Nightmare Disorder (631)
307.46 Sleep Terror Disorder (634)
307.46 Sleepwalking Disorder (639)
307.47 Parasomnia NOS (644)

SLEEP DISORDERS RELATED TO ANOTHER MENTAL DISORDER (645)
327.02 Insomnia Related to . . . *[Indicate the Axis I or Axis II Disorder]* (645)
327.15 Hypersomnia Related to . . . *[Indicate the Axis I or Axis II Disorder]* (645)

OTHER SLEEP DISORDERS (651)

327.xx Sleep Disorder Due to . . . *[Indicate the General Medical Condition]* (651)
- .01 Insomnia Type
- .14 Hypersomnia Type
- .44 Parasomnia Type
- .8 Mixed Type

—.— Substance-Induced Sleep Disorder *(refer to Substance-Related Disorders for substance-specific codes)* (655)

Specify type: Insomnia Type/Hypersomnia Type/Parasomnia Type/Mixed Type
Specify if: With Onset During Intoxication/With Onset During Withdrawal

Impulse-Control Disorders Not Elsewhere Classified (663)

312.34 Intermittent Explosive Disorder (663)
312.32 Kleptomania (667)
312.33 Pyromania (669)
312.31 Pathological Gambling (671)
312.39 Trichotillomania (674)
312.30 Impulse-Control Disorder NOS (677)

Adjustment Disorders (679)

309.xx Adjustment Disorder (679)
- .0 With Depressed Mood
- .24 With Anxiety
- .28 With Mixed Anxiety and Depressed Mood
- .3 With Disturbance of Conduct
- .4 With Mixed Disturbance of Emotions and Conduct
- .9 Unspecified

Specify if: Acute/Chronic

Personality Disorders (685)

Note: These are coded on Axis II.

301.0 Paranoid Personality Disorder (690)
301.20 Schizoid Personality Disorder (694)
301.22 Schizotypal Personality Disorder (697)
301.7 Antisocial Personality Disorder (701)
301.83 Borderline Personality Disorder (706)
301.50 Histrionic Personality Disorder (711)
301.81 Narcissistic Personality Disorder (714)
301.82 Avoidant Personality Disorder (718)
301.6 Dependent Personality Disorder (721)
301.4 Obsessive-Compulsive Personality Disorder (725)
301.9 Personality Disorder NOS (729)

Other Conditions That May Be a Focus of Clinical Attention (731)

PSYCHOLOGICAL FACTORS AFFECTING MEDICAL CONDITION (731)

316 . . . *[Specified Psychological Factor] Affecting . . . [Indicate the General Medical Condition]* (731)
Choose name based on nature of factors:
Mental Disorder Affecting Medical Condition
Psychological Symptoms Affecting Medical Condition

Personality Traits
Style Affecting
Condition
Maladaptive Hea
Affecting Med
Stress-Related Ph
Response Affe
Condition
Other or Unspec
Psychological
Affecting Mec

EDICATION-INDUCE
VEMENT DISORDE
1 Neuroleptic-Ind
Parkinsonism (7
92 Neuroleptic Ma
Syndrome (735)
7 Neuroleptic-In
Dystonia (735)
99 Neuroleptic-In
Akathisia (735)
2 Neuroleptic-In
Dyskinesia (73
Medication-In
Tremor (736)
Medication-In
Disorder NOS

MEDICATIO
DER (736)
Adverse Effe
NOS (736)

ONAL PROB
Relational Pr
Mental Disor
Medical Con
Parent-Child
Problem (73
Partner Rela
(737)
Sibling Rela
Relational P

sorders (685)

ded on Axis II.
Personality Disorder

Personality Disorder

al Personality
(697)
l Personality Disorder

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ic Personality
(714)
Personality Disorder

it Personality
(721)
-Compulsive
y Disorder (725)
y Disorder NOS (729)

ons That May Be a
al Attention (731)

L FACTORS
DICAL CONDITION

al Psychological Factor]
. . [Indicate the General
ndition] (731)
ne based on nature
s:
isorder Affecting
l Condition
gical Symptoms
ng Medical Condition

Personality Traits or Coping Style Affecting Medical Condition
Maladaptive Health Behaviors Affecting Medical Condition
Stress-Related Physiological Response Affecting Medical Condition
Other or Unspecified Psychological Factors Affecting Medical Condition

MEDICATION-INDUCED MOVEMENT DISORDERS (734)

332.1 Neuroleptic-Induced Parkinsonism (735)
333.92 Neuroleptic Malignant Syndrome (735)
333.7 Neuroleptic-Induced Acute Dystonia (735)
333.99 Neuroleptic-Induced Acute Akathisia (735)
333.82 Neuroleptic-Induced Tardive Dyskinesia (736)
333.1 Medication-Induced Postural Tremor (736)
333.90 Medication-Induced Movement Disorder NOS (736)

OTHER MEDICATION-INDUCED DISORDER (736)

995.2 Adverse Effects of Medication NOS (736)

RELATIONAL PROBLEMS (736)

V61.9 Relational Problem Related to a Mental Disorder or General Medical Condition (737)
V61.20 Parent-Child Relational Problem (737)
V61.10 Partner Relational Problem (737)
V61.8 Sibling Relational Problem (737)
V62.81 Relational Problem NOS (737)

PROBLEMS RELATED TO ABUSE OR NEGLECT (738)

V61.21 Physical Abuse of Child (738) *(code 995.54 if focus of attention is on victim)*
V61.21 Sexual Abuse of Child (738) *(code 995.53 if focus of attention is on victim)*
V61.21 Neglect of Child (738) *(code 995.52 if focus of attention is on victim)*
—.— Physical Abuse of Adult (738)
V61.12 (if by partner)
V62.83 (if by person other than partner) *(code 995.81 if focus of attention is on victim)*
—.— Sexual Abuse of Adult (738)
V61.12 (if by partner)
V62.83 (if by person other than partner) *(code 995.83 if focus of attention is on victim)*

ADDITIONAL CONDITIONS THAT MAY BE A FOCUS OF CLINICAL ATTENTION (739)

V15.81 Noncompliance With Treatment (739)
V65.2 Malingering (739)
V71.01 Adult Antisocial Behavior (740)
V71.02 Child or Adolescent Antisocial Behavior (740)
V62.89 Borderline Intellectual Functioning (740)
Note This is coded on Axis II.
780.93 Age-Related Cognitive Decline (740)
V62.82 Bereavement (740)
V62.3 Academic Problem (741)
V62.2 Occupational Problem (741)
313.82 Identity Problem (741)
V62.89 Religious or Spiritual Problem (741)
V62.4 Acculturation Problem (741)
V62.89 Phase of Life Problem (742)

Additional Codes (743)

300.9	Unspecified Mental Disorder (nonpsychotic) (743)
V71.09	No Diagnosis or Condition on Axis I (743)
799.9	Diagnosis or Condition Deferred on Axis I (743)
V71.09	No Diagnosis on Axis II (743)
799.9	Diagnosis Deferred on Axis II (743)

Multiaxial System

Axis I	Clinical Disorders Other Conditions That May Be a Focus of Clinical Attention
Axis II	Personality Disorders Mental Retardation
Axis III	General Medical Conditions
Axis IV	Psychosocial and Environmental Problems
Axis V	Global Assessment of Functioning

Multiaxia

A multiaxial syste
a different domain
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Axis I	Clinic Other
Axis II	Perso Ment
Axis III	Gene
Axis IV	Psych
Axis V	Glob

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EXHIBIT C1

Exhibit C1

Annals of Clinical Psychiatry, Vol. 14, No. 1, March 2002 (© 2002)

A Pilot Placebo-Controlled Study of Fluvoxamine for Pathological Gambling

Carlos Blanco, MD, PhD,[1,2,4] Eva Petkova, PhD,[1,2] Angela Ibáñez, MD, PhD,[3] and Jerónimo Sáiz-Ruiz, MD, PhD[3]

The objective of this study was to evaluate the efficacy of fluvoxamine in the treatment of pathological gambling. Thirty-two patients were treated for 6 months in a double-blind, placebo-controlled study of fluvoxamine 200 mg/day. Outcome measures included reduction in money and time spent gambling per week. Longitudinal mixed effects models and completers analyses were used for estimation and hypothesis testing. Fluvoxamine was not statistically significantly different from placebo in the overall sample. However, fluvoxamine was statistically significantly superior to placebo in males and in younger patients. The power of the study was limited by the high (59%) placebo-response rate. Fluvoxamine may be a useful treatment for certain subgroups of patients with pathological gambling. Several methodological recommendations are made for future pharmacological trials of pathological gambling.

KEY WORDS: impulse control disorder; fluvoxamine; pathological gambling; serotonin reuptake inhibitors.

INTRODUCTION

Epidemiological studies suggest that pathological gambling has a prevalence of 1.1–1.5% in the adult population (1, 2). In the absence of treatment, pathological gambling is characterized by a chronic, progressive course, and it is associated with high levels of personal and family suffering and substantial economic cost to the individual and society (3). When they seek treatment, pathological gamblers have high dropout rates, and rarely remain abstinent over time (4, 5).

Previous studies have suggested that pathological gamblers have abnormal serotonergic function. Pathological gamblers have low baseline serum prolactin with blunted response to intravenous clomipramine (6), increased serum prolactin response to m-CPP (7), and low platelet monoamine oxidase activity (8). Recently, we showed an association between the less efficient variant of a polymorphism at the serotonin transporter gene and male pathological gamblers that may have functional significance (9). There is also emerging evidence that prevalence and correlates of pathological gambling may be different between male and females (10, 11), as well as across ages (1, 2), suggesting that different subgroups of pathological gamblers may show a differential response to treatment. A single-blind and a placebo-controlled, cross-over study have suggested that fluvoxamine is efficacious in the acute treatment of pathological gambling (4, 12), whereas recent results suggest that the opioid antagonist naltrexone (5) may also be effective in the acute treatment of pathological gambling. We report the results of the first double-blind, parallel, placebo-controlled study for the treatment of pathological gambling over a period of 6 months, and explore the presence of potential predictors of treatment response.

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METHODS

Patient Population

Thirty-two patients were recruited from the Pathological Gambling Outpatient Program of the Department of Psychiatry of Hospital Ramón y Cajal in Madrid, Spain. The Institutional Review Board of Hospital Ramón y Cajal approved the protocol prior to the beginning of the study. All subjects met *DSM-III-R* criteria for pathological gambling and signed informed consent prior to their entry in the study. Patients were excluded if they met criteria for another axis I diagnosis, including any substance abuse (except nicotine dependence) in the Structured Clinical Interview for *DSM-III-R*, or had any unstable medical condition.

Study Design

Patients were randomly assigned to fluvoxamine or placebo and treated for 6 months using a double-blind, placebo-controlled, parallel groups design. The dose of fluvoxamine was 100 mg/day given in a single dose during the first 2 weeks, and 200 mg/day (100 mg b.i.d.) for the rest of the trial. This dose is similar to the average doses used in previously published trials of fluvoxamine for pathological gambling (4, 12). Patients were allowed to use clorazepate (a benzodiazepine) 5–15 mg/day for anxiety or insomnia, and domperidone (an antiemetic medication) 10–30 mg/day for nausea. No other psychotropic medications were allowed during the study. All patients were encouraged to attend self-help or therapy groups focused on pathological gambling.

Symptom Assessment

The primary outcome measure for the study was the change in the average amount of money spent on gambling per week in the last month, or the last 2 weeks for the 2-week assessment (visit 2). Number of hours per week spent gambling was considered a secondary outcome measure. Patients were assessed at baseline, at 2 weeks, 4 weeks, and then monthly until the end of the study. Baseline assessments included current age, age of onset of the disorder, total duration of gambling in years, money and time per week spent gambling over the last month, and number of days abstinent prior to first medication visit.

Statistical Analysis

The principal analysis for the study was linear mixed effects models (LMEM) (13). LMEM, a type of intent-to-treat analysis, has several advantages over analysis of variance with repeated measures in the analysis of longitudinal data: 1) It allows for the use of all available data from all subjects, regardless of whether or not they have a complete set of observations; 2) It does not require equal time intervals between successive measurements for all subjects; 3) It possesses flexible tools to account for the correlation structure of the repeated measurements by including random effects (14).

The following models were fit:

$$\text{(a) } Y = \beta_0 + \beta_1 \text{drug} + \beta_2 \text{time} + \beta_3 \text{drug} \times \text{time} + \text{error}$$

and

$$\text{(b) } Y = \beta_0 + \beta_1 \text{drug} + \beta_2 \text{time} + \beta_3 \text{drug} \times \text{time} + \beta_4 \text{covariate} + \beta_5 \text{drug} \times \text{covariate} + \beta_6 \text{time} \times \text{covariate} + \beta_7 \text{drug} \times \text{time} \times \text{covariate} + \text{error},$$

where Y represents the outcome measure, and age and sex were considered as possible factors influencing the outcome (covariates). Outcome variables that did not follow a normal distribution were log-transformed to stabilize their variance prior to model-fitting.

Models with and without covariates were fitted for money and hours per week spent gambling as the outcome measures. To investigate the effect of the covariates and their interaction with time and treatment on the outcome, models initially including all covariates were fitted, and backward elimination was employed to exclude terms that were not statistically significant at the $\alpha = 0.05$ (two-tailed) level. When interaction terms were statistically significant, according to the hierarchical principle of modeling, all lower order terms involved in the interaction were retained in the model regardless of their p values (14).

Additionally, the completers analysis for the "money" variable, and a comparison of the percent responders in the two treatment groups are presented (results for the other variables are available upon request). A patient was considered responder if he/she reported abstinence at the end of the study or at the time of last observation. All results are considered significant at the $\alpha = 0.05$ (two-tailed) level.

Table 1. Baseline Characteristics of Pathological Gamblers

Characteristic	Fluvoxamine	Placebo	Analysis
N	15	17	
Gender (% male)	67	65	$\chi^2 = 0.01$, df = 1, $p = 0.9$
Age (SD)	42.3 (12.7)	41.9 (11.1)	$t = 0.11$, df = 30, $p = 0.9$
Age of onset of pathological gambling (SD)	31.7 (12.6)	34.18 (10.24)	$t = -0.60$, df = 30, $p = 0.6$
Days of abstinence prior to entry in study	14.6 (8.9)	10.1 (9.3)	$t = 1.39$, df = 30, $p = 0.2$
Money (US$)/week[a]	509 (1252)	244 (243)	$t = 0.58$, df = 30, $p = 0.6$
Hours/week[a]	19.1 (20.2)	14.9 (11.8)	$t = 0.70$, df = 30, $p = 0.5$

[a] Outcome measures, assessed also on the seven follow-up visits.

RESULTS

As shown in Table 1, patients in the placebo and fluvoxamine groups were similar at baseline in all demographic characteristics and severity measures.

Linear Mixed Effects Models

Gambling behavior for both groups decreased over the course of the study as measured by amount of money and number of hours per week spent on gambling. The decrease was faster for subjects on fluvoxamine than on placebo (Fig. 1(a)), but failed to reach statistical significance in the unadjusted (i.e., without covariates) models. However, as shown in Table 2, there were statistically significant differences between subjects on fluvoxamine and placebo with respect to the speed of decrease of money spent per week when adjusting for gender, as indicated by the *p* value of the interaction term "Drug × Time × Sex". Male patients had a faster response on drug than on placebo, while there was no differential effect of drug and placebo in female patients (Fig. 1(b)).

Similarly, statistically significant differences between the speed of decline on fluvoxamine and placebo were present when considering the time spent gambling and adjusting for age. Younger patients benefited more from fluvoxamine treatment than older ones on measures of time spent gambling (Fig. 1(c)). Gender did not influence the results of this outcome variable.

Completers Analysis

Table 3 presents the results from the dichotomous outcome variable gamble/did-not-gamble at all

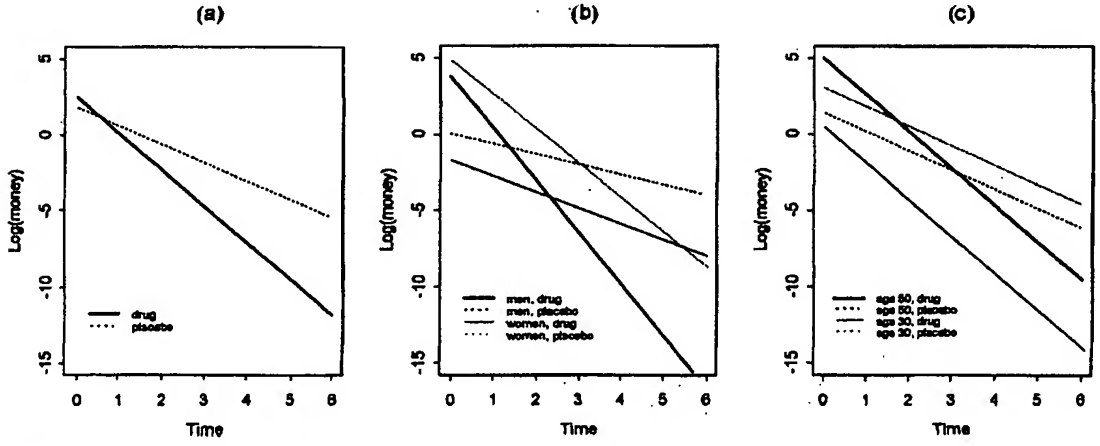

Fig. 1. Course of improvement in gambling behavior. Effect of time in treatment on money spent on gambling (a) by drug and no covariates, (b) by drug and gender, and (c) by drug and age.

Table 2. Results From Fitting Linear Mixed Effects Models

	Model						
Response variable	Drug [β_1 (SE) p-value]	Time [β_2 (SE) p-value]	Drug × Time [β_3 (SE) p-value]	Covariate [β_4 (SE) p-value]	Drug × Covariate [β_5 (SE) p-value]	Time × Covariate [β_6 (SE) p-value]	Drug × Time × Covariate [β_7 (SE) p-value]
Money spent weekly							
No covariate	0.7 (2.3)	−1.2 (0.4)	−1.2 (0.7)				
	$p = 0.8$	$p = 0.005$	$p = 0.09^a$				
Age	−11.9 (6.4)	−1.3 (0.4)	−1.2 (0.7)	−0.1 (0.1)	0.3 (0.1)		
	$p = 0.06$	$p = 0.005$	$p = 0.1$	$p = 0.45$	$p = 0.03^a$		
Sex	3.8 (2.7)	−.67 (0.48)	−2.7 (0.96)	4.8 (2.8)	−10.3 (4.8)	−1.6 (0.9)	4.0 (1.5)
$M = 0$, $F = 1$	$p = 0.2$	$p = 0.2$	$p = 0.005$	$p = 0.09$	$p = 0.03$	$p = 0.06$	$p = 0.01^a$
Hours spent weekly							
None	0.2 (1.9)	−1.2 (0.6)	−0.9 (0.3)				
	$p = 0.93$	$p = 0.005$	$p = 0.16^a$				
Age	0.45 (1.92)	−3.29 (1.16)	−1.28 (0.65)	−0.06 (0.08)	0.05 (0.03)		
	$p = 0.81$	$p = 0.005$	$p = 0.05$	$p = 0.5$	$p = 0.05^a$		
Sex[b]							

[a] Highest order (interaction) term in the model. When an interaction term is statistically significant, according to the hierarchical principle of modeling, all lower order terms that are involved in the interaction are retained in the model regardless of their p-values (13).
[b] No term in the model was significantly different from zero. The model is then reduced to model with no covariates.

available time-points of the study are presented. At each time point there was a higher proportion of responders on fluvoxamine than on placebo, but the differences did not reach statistical significance. Similarly, when response was defined as abstinence from gambling in the last three visits, there were no significant differences between the placebo and fluvoxamine groups (41% vs. 33%, $\chi^2 = 0.2$, df $= 1$, $p = 0.6$).

Dropouts and Adverse Effects

More people dropped out from the fluvoxamine group than from the placebo group, but the difference in attrition was not statistically significant. Seven patients in the fluvoxamine group and four in the placebo group were terminated prematurely from the protocol owing to lack of compliance. Three patients on fluvoxamine and one in placebo dropped out owing to side effects of the medication and one patient on placebo dropped out owing to symptomatic improvement. Two patients on fluvoxamine and one on placebo dropped out for unknown reasons and could not be located despite repeated efforts to contact them. There were no statistically significant differences between the groups in the reasons for dropout.

The most frequent side effects were insomnia (53% in the placebo group vs. 33% in the fluvoxamine group), dizziness (29 vs. 33%), headache (29 vs. 33%), diarrhea (23 vs. 37%), weight loss (29 vs. 27%), and nausea (12 vs. 41%). Only nausea was reported significantly more often in the fluvoxamine than in the placebo group (46.7 vs. 11.8%, $\chi^2 = 4.8$, df $= 1$, $p = 0.03$).

There was no difference in the use of medications. Five patients in the placebo group used a benzodiazepines at some point during the study, compared to three in the fluvoxamine group (29.4 vs. 20%,

Table 3. Completers Analysis

Time in treatment trial	Subjects on drug	Responders (%)[a]	Subjects on placebo	Responders (%)	Analysis
At least 2 weeks	15	73	17	59	$\chi^2 = 0.7$, df $= 1$, $p = 0.39$
At least 1 month	11	73	17	59	$\chi^2 = 0.6$, df $= 1$, $p = 0.45$
At least 2 months	11	73	15	53	$\chi^2 = 1.0$, df $= 1$, $p = 0.32$
At least 3 months	6	83	15	53	$\chi^2 = 1.6$, df $= 1$, $p = 0.20$
At least 4 months	4	75	13	54	$P^b = 0.6$, df $= 1$, $p = 0.45$
At least 5 months	4	75	11	45	$P^b = 1.0$, df $= 1$, $p = 0.31$
Six months (full trial)	3	100	10	10	$P^b = 2.4$, df $= 1$, $p = 0.12$

[a] Responder is defined as someone who reported abstinence from gambling since the prior visit.
[b] Fisher's exact test.

$\chi^2 = 0.4$, df = 1, $p = 0.5$). Similarly, two patients in the placebo group took at least a dose of domperidone compared to four in the fluvoxamine group (11.8 vs. 26.7%, $\chi^2 = 0.4$, df = 1, $p = 0.3$).

DISCUSSION

There were no significant differences in the proportion of responders between patients treated with fluvoxamine and those assigned to placebo for the overall trial. However, in the more powerful LMEM models the rate of decline of dollars spent on gambling approached significance ($p < 0.09$) in the unadjusted model, and became significant when gender and age were entered in the model. This discrepancy in the results of the categorical and dimensional analysis was partly due to the small sample size of the study, which limited the power of the test for difference between proportions. In addition, there was an unexpectedly high placebo-response rate. Based on previous case reports that had suggested poor response of pathological gambling to placebo (15, 16), when planning the study we had estimated that with a placebo response of 30% and a drug response of 60%, we would have a power of 90% to detect a statistically significant difference in the number of responders. In contrast, a post hoc analysis showed that, with our sample size and given the placebo response rate of 59% in the intent to treat sample in the current study, a response rate of 99% in the fluvoxamine group would have been needed to have a power of 80% to detect a statistically significant difference between the two groups. The results of the single-blind trial of fluvoxamine (4) also suggest that placebo response in pathological gambling may be higher than previously estimated. Placebo run-in periods may be necessary to increase the power of pharmacological trials in pathological gambling.

The reasons for this high placebo response rate are unclear and deserve further study. It is possible that periodic visits to the treating physicians may have had higher therapeutic potential than anticipated. Patients may have also benefited from attending self-help and therapy groups, although no systematic data were collected that would allow their inclusion as a covariate in our analyses. The fact that time in treatment was consistently associated with better outcome in both the placebo and fluvoxamine groups seems to support that interpretation. Future studies should investigate whether attendance to Gamblers Anonymous or therapy groups exerts any effect (additive or synergistic) in the outcome of drug treatment of pathological gambling. Preliminary findings suggest that combined drug and psychotherapy may be superior to psychotherapy alone in the treatment of pathological gambling (De la Gándara JJ. Fluoxetine: open trial in pathological gambling, presented at the 152nd Annual Meeting of the American Psychiatric Association, Washington, DC, 1999). Similar results have been recently documented in a study of binge eating disorder (17), which like pathological gambling, has sometimes been conceptualized as an obsessive–compulsive (OCD) spectrum disorder (18). Emerging evidence indicates that pathological gambling may share more features with addictive than with OCD-spectrum disorders (19, 20), suggesting that the superiority of combined treatment over medication or therapy alone may extend across diagnostic categories.

The finding that the percentage of responders in the fluvoxamine group increased throughout the trial, while the opposite happened in the placebo group also suggests that fluvoxamine may be an effective treatment for pathological gambling. Our finding is consistent with Hollander *et al.*'s cross-over trial (12), which found a more persistent response to fluvoxamine than to placebo. However, both findings need to be interpreted with caution: In Hollander's study, the duration of each phase was relatively brief (8 weeks) while in our study there was a high rate of attrition over the 6 months. More than 50% of the patients in both groups that did not complete our protocol had to be terminated prematurely from the study owing to lack of compliance, despite a decrease in their amount of time and money spent on gambling. Retention of patients in treatment is one of the most pressing challenges when working with this population. The single-blind study by Hollander *et al.* (4) showed a 38% (6 out of 16) dropout rate in the placebo lead-in phase, whereas only 66% (10 out of 15) completed the cross-over study. Preliminary data from other pharmacological studies also suggest high dropout rates (5, 12), indicating the difficulty of retaining in treatment this patient population. Similarly, in the only published controlled trial of psychotherapy study of pathological gambling 8 out of 22 patients in the active treatment group and 3 out of 18 in the waiting list used as control group dropped out before the end of the study (21). Use of techniques that may increase retention, such as motivational interviewing (22) or network therapy (23) may improve adherence to treatment and overall outcomes. Placebo-controlled studies that include a psychotherapy in

both arms of their design are gaining acceptance in the field of substance abuse as a method to potentiate the effect of the drug and increase abstinence (24), and may be similarly useful in the treatment of pathological gambling. The de la Gándara study suggests that combined treatment may be superior to monotherapy.

The fact that male, but not female, patients on fluvoxamine had a faster and more pronounced decrease in the amount of money spent weekly on gambling than those on placebo is interesting but requires replication. The reasons for this gender difference are unclear. Male and female pathological gamblers have numerous clinical and genetic differences (25, 26) that may influence the course of the disorder and its response to treatment. Several studies have suggested that the serotonergic system might be dysregulated in pathological gamblers. However, these studies have been carried out in samples composed exclusively (7, 8) or predominantly of men (6). Whether those findings extend to women remains unknown. However, male and female pathological gamblers have substantial differences in their gambling behaviors and psychological characteristics (10, 11), and a less intense serotonergic dysregulation in female gamblers has been suggested as a factor in the lower prevalence of pathological gambling of women compared to men (8). In a recent study we found that males, but not female, pathological gamblers had a significantly higher frequency than the comparison group of the less efficient allele of a functional polymorphism located in the promoter region at the serotonin transporter (5-*HTT*) gene (9), leading to a poorer functioning of the gene. This finding is particularly interesting since 5-*HTT* mediates the mechanism of action of SSRIs, including fluvoxamine. Whether there is a connection between the gender-specific efficacy of fluvoxamine in pathological gambling and the gene deficiency is unknown and deserves further study. Pathological gambling also has high comorbidity with depression (27). Although patients were excluded from the study if they met criteria for major depressive disorder, it is possible that subclinical symptoms of depression might have been unequally distributed between the genders and affected the outcome in either direction. The discrepancy in the gender response could also derive from the association of pathological gambling with dysregulated noradrenergic and dopaminergic neurotransmitter systems (28, 29). Finally, because blood levels of fluvoxamine were not measured during the trial, the possibility that differences in such blood levels account for the gender differences in response cannot be ruled out.

The reasons for a better response in younger patients remain unclear and deserve further study. However, elderly depressed patients treated with SSRIs also appear to have lower response rates than younger adults (30), suggesting that age-related changes in the serotonergic system may substantially influence the effect of SSRIs. Alternatively, it is possible that changes in motivation are more difficult to achieve at a later age, probably due in part to the longer gambling careers of older patients.

CONCLUSION

There are currently no established treatments for pathological gambling. A few reports have suggested that a variety of treatment modalities may benefit some patients (14, 15, 21, 31–34), but more definitive controlled clinical trials are needed to confirm and quantify the efficacy of those strategies. Our study, partially supporting the findings of Hollander *et al.* (4, 12), suggests that fluvoxamine may be efficacious in the treatment of at least a subgroup of pathological gamblers. However, more studies with larger samples are needed before the efficacy of fluvoxamine can be confirmed.

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Exhibit C1

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Placebo-Controlled Study of Fluvoxamine in the Treatment of Patients With Compulsive Buying

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Outline

Graphics

Abstract

Compulsive buying is a syndrome characterized by the impulsive and/or compulsive buying of unneeded objects that results in personal distress, impairment in vocational or social functioning, and/or financial problems. Results from a two-site, double-blind, placebo-controlled 13-week trial of fluvoxamine are presented. Subjects had problematic buying behavior that they could not control for the previous 6 months or longer and met DSM-IV criteria for impulse control disorder-not other-wise specified (ICD-NOS) and the University of Cincinnati criteria for compulsive buying. Assessments included clinician-rated scales-the Yale-Brown Obsessive Compulsive Scale modified for compulsive buying, the Clinical Global Impression Scale, the Global Assessment of Functioning, and the Hamilton Rating Scale for Depression-and patient self-reports using daily diaries, which measured episodes of compulsive buying. Forty-two subjects gave informed consent, with 37 subjects providing evaluable information and 23 completing the study. Current or past psychiatric comorbidity was present in 74% of subjects. Intent-to-treat and completer analyses failed to show a significant difference between treatments on any measures of outcome. A high placebo-response rate, possibly from the behavioral benefits of maintaining a daily diary, prevents any definitive statement on the efficacy of fluvoxamine in treating compulsive buying.

COMPULSIVE BUYING AS A clinical syndrome is characterized by the impulsive and/or compulsive buying of unneeded objects that results in personal distress, impairment in vocational or social functioning, and/or financial problems.1-3 In DSM-IV terms, it is classified as an impulse control disorder-not otherwise specified (ICD-NOS), which codes for disorders of impulse control that do not meet the criteria for any of the specific impulse-control disorders described in DSM-IV. The essential feature of an impulse control disorder (ICD) is the failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others. The individual usually feels an increasing sense of tension or arousal before committing the act, and then experiences pleasure, gratification, or relief at the time of committing the act. McElroy and colleagues 2 developed the University of Cincinnati (UC) diagnostic criteria, which operationally defines compulsive buying.

The difference between compulsive buyers and normal shoppers seems to be qualitative rather than simply quantitative. Because shopping sprees are a symptom seen in hypomania and mania, compulsive buying has to be present outside of such mood states for the diagnosis. It is estimated that the incidence of compulsive buying in the general population is 1.1% to 5.9% based on its definition.4-7 Available data suggest that compulsive buying is associated with significant morbidity, including family dysfunction, indebtedness, and even bankruptcy. Compulsive buying is associated with other forms of psychopathology-particularly mood disorders, obsessive-compulsive disorder, eating disorders, and ICDs.8, 9 Compulsive buying may respond to treatment with antidepressants that enhance serotonergic neurotransmission.10 An open trial of fluvoxamine in compulsive buying reported significant benefits by reducing symptomatology.11 We report the first placebo-controlled treatment trial of a medication in the treatment of patients with compulsive buying.

Methods

This study evaluated the efficacy and safety of fluvoxamine (Luvox, Solvay Pharmaceuticals, Marietta, GA) in a double-blind, placebo-controlled, parallel-group trial of outpatients with compulsive buying. The study was conducted at two university sites: Emory University and UC. Our sources for patients included clinic referrals, responses to news releases, and advertisements in local media.

Inclusion and exclusion criteria

Male and female outpatients aged 18 to 65 years with problematic buying behavior were screened initially over the telephone. Eligible patients gave informed consent and were interviewed using a structured psychiatric interview (Structured Clinical Interview for DSM-IV) at the screening visit. Patients who met the *DSM-IV* definition of ICD-NOS and UC diagnostic criteria for compulsive buying were eligible to enter the study. Patients were required to have displayed problematic buying behavior, which they could not control, for the previous 6 months or longer.

Exclusionary criteria were a lifetime history of psychosis, hypomania, or mania; psychoactive substance dependence in the past 6 months; clinically assessed current risk of suicidality; unstable medical conditions; and current pregnancy or nursing. Patients receiving weekly psychotherapy for more than 3 months before the study were allowed to enter the study as long as they agreed to continue the psychotherapy without a change in its frequency for the duration of the study. Patients were free of psychotropic medicines for at least 1 week before study entry (longer for medications with prolonged half-lives).

Assessments

All patients underwent a physical examination, and routine laboratory values including an electrocardiogram were obtained at the screening visit. Compulsive buying was assessed using the Yale-Brown Obsessive Compulsive Scale modified for compulsive buying (YBOCS-CB), the Clinical Global Impression Scale (CGI), the Global Assessment of Functioning (GAF), the Hamilton Rating Scale for Depression (HAM-D), and daily patient diaries, which measured the number of buying or shopping episodes per week, the amount of time spent buying or shopping per week, and the amount of money spent on compulsive buying per week. Adverse events were elicited by general inquiry. Vital signs were monitored at each visit.

Procedure

After the screening interview, patients entered a 1-week single-blind placebo treatment before baseline assessments were determined. Patients who demonstrated a greater than 50% improvement in their YBOCS-CB scores were excluded. Patients were then randomly assigned to receive 12 weeks of double-blind fluvoxamine or placebo. Fluvoxamine or placebo was started at 50 mg and was increased weekly up to 300 mg (six capsules given in two divided doses) according to the patient's response and report of side effects. If a patient was unable to tolerate any side effect, the dosage could be decreased. Patients were seen weekly for the initial 5 weeks, and then every 2 weeks.

Statistical analyses

Accuracy of data entry was ensured by using double-key entry with forced correction for initial input followed by the validation of a sample of entries against the original data sheets. Data were then converted to SAS data sets, at which time the treatment blind was broken.

Two primary sets of inferential analyses were conducted. The first was an intent-to-treat analysis that included all subjects who completed at least one visit subsequent to randomization. These analyses used a last-observation-carried-forward (LOCF) approach to missing data. The primary analyses were repeated-measures analyses of variance (ANOVAs) computed using SAS Proc GLM for continuous variables and the Fisher exact test for categorical outcome measures taken from the last visit. The second set of analyses was of study completers, defined as those who completed a minimum of 10 weeks of double-blind treatment. For continuous variables, analyses were conducted using random regression models that were computed using SAS Proc MIXED. For these analyses, both the time on protocol and the outcome measures were log-transformed for linearization on the basis of residual plots.

Results

Demographics

Forty-two patients gave informed consent for participation in the study. Their average age was 40.9 (±9.4) years. Thirty-four (81%) were women and 38 (90%) were white. Five terminated before a postrandomization assessment. Thus, 37 patients were included in the intent-to-treat (with LOCF) analysis. Twenty-three patients completed the study. Reasons for early termination were adverse events (N = 8), non-drug-related reasons (N = 5), loss to follow-up (N = 5), and protocol violation (N = 1).

Comorbidity

Comorbid psychiatric diagnoses were present in 31 (74%) of 42 patients. Twenty-five (60%) had more than one comorbid diagnosis. The majority were depressive disorders followed by anxiety disorders and substance abuse/dependence (Table 1).

Table 1. Lifetime comorbid DSM-IV diagnoses on the Structured Clinical Interview for DSM-IV (N = 42)[a]

Response to treatment

The average dose for fluvoxamine was 215 mg (±76.5 SD) and for placebo was the equivalent of 270 mg (±75 SD). Gastrointestinal distress (25%) and insomnia (20%) were the most common adverse effects reported with fluvoxamine, whereas headache (29%) and sedation (18%) occurred with placebo.

Table 2 represents the intent-to-treat analysis with LOCF. A repeated-measures ANOVA found that each of the dependent variables improved with time at a significant level, but time × site, time × group, and time × group × site were not significantly different. An analysis of completers found highly significant improvement over time ($p < 0.001$) for the YBOCS-CB total score, GAF score, and HAM-D score, but no terms for change over time involving treatment or site were significant ($p > 0.2$ for all).

Table 2. Treatment outcome[a]

For the diary data, random regression models found no significant effects of time, site, or treatment on the number of shopping episodes, amount of time spent shopping, amount of money spent, or number of items purchased for the intent-to-treat sample. For the sample of study completers, the number of shopping episodes ($p = 0.049$) and the number of items purchased ($p = 0.028$) declined significantly over time, but there were no significant effects of site or treatment ($p > 0.1$ for all other terms and variables). An analysis of the categorical response, defined as a CGI improvement score of 2 or less, was not significant with respect to treatment in either the intent-to-treat sample (9/20 vs. 8/17 responders for fluvoxamine and placebo, respectively; Fisher exact $p > 0.99$) or study completers (6/11 vs. 7/12 responders, for fluvoxamine and placebo, respectively; Fisher exact $p > 0.99$).

Discussion

Compulsive buying is deserving of study given its prevalence and degree of distressing consequences. Compulsive buying, although definable by behavioral manifestations, may have varying underlying motivational, emotional, and reinforcing characteristics suggestive of heterogeneity. Qualitative differences exist among compulsive buyers; for example, those shopping on television might be different from shoppers at yard sales or individuals who buy big-ticket, costly items. Such phenomenologic issues are beginning to be explored.12

This study population had high psychiatric comorbidity, which is consistent with the literature on compulsive buying 7-9, 13 as well as pathologic gambling.14 The most common comorbid conditions were affective disorders, predominantly major depression. Anxiety disorders, eating disorders, and substance use disorders were also present. Comorbidity can be considered a marker for greater severity of illness. However, it can also be argued, given the high comorbidity of psychopathology, that compulsive buying is a symptom complex seen in several conditions rather than a separate syndrome. Repetitive behaviors that are cued by urges might have a common underlying neurobiologic mechanism, which is speculated to be mediated through the genetic polymorphism of the dopamine D_4 receptor.15

ICDs have several unique characteristics that make controlled trials challenging. ICDs, in particular, may be characterized by a tendency to transiently reduce the behavior when greater attention is focused on it. Thus, open-label trials can have a potential bias toward success, whereas controlled trials are more likely to measure the true effect of the active treatment.

Performing clinical trials in this population is also a challenge. Subjects were initially enthusiastic about considering their compulsive buying within a diagnostic perspective, but with time and breakthrough buying, they struggled with their sense of shame and failure. Several patients were initially enthusiastic but inconsistent as the study progressed. They were emotionally reactive to their daily level of symptomatology, unable to take a longer-term perspective, and unwilling to accept partial improvement. Furthermore, several were intolerant of even minimal side effects. Thus, of the 42 who gave informed consent, only 23 subjects completed the study.

The assessment of compulsive buying is problematic. The weekly rating scales are based largely on self-report to the clinician. Daily diaries kept by the patients showed considerable variability from day to day. The psychometrics of the scales used in the assessment of compulsive buying are beginning to be assessed.16

A previous open-label trial of fluvoxamine, a selective serotonin reuptake inhibitor, documented benefits in treating this population.11 In the present study, although fluvoxamine significantly reduced compulsive buying during 12 weeks of active treatment, there was also a comparable response to placebo. The robust placebo response would indicate that nonspecific factors had beneficial effects. However, ICDs are also responsive to behavioral interventions. It could be that the benefits of maintaining a daily diary to monitor symptoms might itself have significant benefit. The daily diary, therefore, might have been covert cognitive behavioral therapy, contributing significantly to the "placebo" response.

This study emphasizes the importance of placebo-controlled studies of compulsive buying. This study can provide no opinion on the efficacy of fluvoxamine as a treatment for compulsive buying, given the prominent benefits of placebo treatment (which included daily self-monitoring of the buying urges and behavior). Further studies with a larger number of patients and a modified trial design are indicated. Future pharmacologic studies should incorporate a longer lead-in period with behavioral monitoring using daily diaries before initiating active treatment. Examining the efficacy of cognitive behavioral therapy in controlled trials is also encouraged, given the powerful effect that is potentially attributable to simple behavioral monitoring. For the clinician, current management of individuals with compulsive buying should include daily self-monitoring using a diary.

Acknowledgment

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EXHIBIT D1

Exhibit D1

Paroxetine treatment of pathological gambling: a multi-centre randomized controlled trial

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Previous studies have suggested the efficacy of serotonergic agents in the treatment of pathological gambling. The aim of the present study was to determine whether treatment with paroxetine in a large sample of subjects with pathological gambling would effectively diminish the severity of gambling symptoms. A 16-week, double-blind, placebo-controlled trial was conducted at five outpatient academic research centres in two countries (USA and Spain). Seventy-six outpatients (mean age 45.4 ± 10.6 years; 30 women, 46 men) with pathological gambling were randomized to acute treatment with paroxetine in flexible daily dosages of 10–60 mg/day ($n=36$) or placebo ($n=40$). The primary outcome measure was the Clinical Global Impressions scale. Both the paroxetine- and the placebo-treated groups demonstrated comparable improvement at 16 weeks (59% response rate in the paroxetine group, 48% rate in the placebo group; chi squared = 0.737; d.f. = 1; $P=0.390$). Paroxetine consistently resulted in a greater percentage of responders at each study visit compared to placebo but failed to demonstrate statistical superiority to placebo on scores on the Clinical Global Impressions scale, the Yale–Brown Obsessive–Compulsive Scale Modified for Pathological Gambling, or the Gambling Symptom Assessment Scale. High rates of symptom improvement were observed in pathological gamblers receiving either paroxetine or placebo after 16 weeks. Paroxetine consistently demonstrated an advantage over placebo on the Clinical Global Impressions scale; however, a larger sample size may have registered significant differences. *Int Clin Psychopharmacol* **18:243–249 © 2003 Lippincott Williams & Wilkins.**

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Introduction

Pathological gambling is a significant public health problem that often results in a distinctive pattern of persistent and disabling psychological symptoms. Although once thought to be relatively uncommon, recent studies estimate that pathological gambling has a lifetime prevalence among adults of 1.6% (Shaffer and Hall, 1996; Shaffer *et al.*, 1999). The disorder is associated with high rates of lifetime psychiatric comorbidity, including major depression and alcohol or substance abuse and dependence (McCormick *et al.*, 1984; Roy *et al.*, 1988; Black and Moyer, 1998; Ibanez *et al.*, 2001). Pathological gamblers are prone to financial losses that often lead to bankruptcy, divorce and/or criminal behaviour (Blaszczynski and Silove, 1996; Grant and Kim, 2001).

Pathological gambling is categorized as an impulse control disorder. Several studies in human and non-human primates have found reduced serotonin function in the brain to be associated with impulsivity and aggression (Moreno *et al.*, 1991; Doudet *et al.*, 1995; Mehlman *et al.*, 1995; Virkkunen *et al.*, 1995; Coccaro, 1996; DeCaria *et al.*, 1998). As such, drugs that target serotonin systems have the potential value to ameliorate symptoms of behavioural dyscontrol, including gambling behaviours.

A small number of studies have tested serotonergic agents as a treatment for pathological gambling. One single-blind study using fluvoxamine reported seven of 10 patients as treatment responders using the Clinical Global Impression–Improvement scale assessing pathological gambling symptoms (PG-CGI-I) (Hollander *et al.*, 1998). In a double-blind study of 15 subjects, fluvoxamine resulted in statistically significant reduction on the PG-CGI-I scale compared to placebo, although reductions in the total score of the Yale–Brown Obsessive–Compulsive Scale modified for Pathological Gambling (PG-YBOCS) between the groups did not reach statistical significance (Hollander *et al.*, 2000). A third fluvoxamine

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study ($n = 34$) found significantly greater reductions in time and money spent gambling per week, but only in male and young pathological gamblers treated with medication (Blanco *et al.*, 2002). In an open-label study of citalopram, seven of eight patients were rated as responders according to the PG-CGI-I after 12 weeks of treatment (Zimmerman *et al.*, 2002).

Paroxetine has also demonstrated efficacy in treating pathological gambling. In an 8-week, double-blind study of paroxetine, significantly greater reductions in the total score of the Gambling Symptom Assessment Scale (G-SAS) were observed in the paroxetine group compared to the placebo group at study end (Kim *et al.*, 2002). In this study of 55 subjects, a significantly greater number of the patients in the paroxetine group achieved a response, which was rated as 'much improved' or 'very much improved' on the PG-CGI-I (60.8% compared to 22.7% on placebo).

Despite the initial promise of these early studies, they were limited by small sample sizes recruited from individual geographical locations. As such, their findings may be influenced by differences in local gambling regulations or subject characteristics. To examine further the tolerability and efficacy of paroxetine in the treatment of pathological gambling, we conducted a multicentre, placebo-controlled study. Because of the substantial impairment in functioning associated with pathological gambling, psychosocial and symptomatic outcomes were assessed. We hypothesized that paroxetine would not only improve the overall functioning of patients suffering from pathological gambling but also reduce the frequency and severity of gambling symptoms.

Methods

Subjects

The subjects were male and female outpatients, aged 18 years and older, who met DSM-IV criteria (APA, 1993) for a principal diagnosis of pathological gambling. Patients were recruited by newspaper advertisements and by referrals for medication treatment. A minimum score of ≥ 5 on the South Oaks Gambling Screen (SOGS) (Lesieur and Blume, 1987) was required. Women's participation was contingent upon negative results of a beta-human chorionic gonadotropin pregnancy test and stable use of a medically accepted form of contraception.

Exclusion criteria were: (i) current Axis I disorder as determined by the Structured Clinical Interview of DSM-IV (SCID) (First *et al.*, 1995), except for nicotine dependence or simple phobia; (ii) a past history of bipolar disorder, schizophrenia, or other psychotic disorder; (iii) alcohol or substance dependence or abuse in the past 3 months; or (iv) baseline scores greater than 18 on either the 17-item Hamilton Rating Scale for Depression or the Hamilton Rating Scale for Anxiety (HAM-D, HAM-A) (Hamilton, 1959, 1960). Concomitant psychotropic medication was not allowed. Patients undergoing individual or group psychotherapy or participating in Gamblers Anonymous were excluded. Individuals with an unstable coexisting medical condition were not eligible for the study.

The research was conducted at outpatient clinics in five academic medical centres from June 2000 to March 2002. The institutional review board at each of the centres approved the study. Potential risks of the study, as well as alternative treatments, were discussed with subjects. After complete description of the study to the subjects, and allowing subjects to ask questions about the study, written informed consent was obtained.

Study design

Patients eligible for the study entered a 1-week, placebo run-in phase. Patients reporting a 30% or greater reduction in the score of the PG-YBOCS (Hollander *et al.*, 1998, 2000) between initial and randomization visits were deemed 'placebo responders' and were not randomized. At the second (baseline) visit, patients were randomized 1:1 to 16 weeks of double-blind treatment with either paroxetine or matched placebo. Randomization for all sites was performed by a technician with no clinical contact who kept the code during the trial. Following randomization, treatment was initiated at 10 mg/day paroxetine or placebo equivalent during week 1 and 20 mg/day during week 2 with flexible dosing up to 60 mg/day, based on clinical response and tolerability. Dosing changes were made in 10 mg increments at weekly intervals. Reductions in the dosage of study medication to the next previous level were allowed if a patient was experiencing a side-effect; once the side-effect subsided, the dosage could be returned to the previous level. Subjects who missed three consecutive doses were discontinued from the study.

Screening and baseline assessments

Patients were evaluated at entry by a semistructured psychiatric interview for pathological gambling and by SCID to assess psychiatric comorbidity. Medical history, physical examination, electrocardiogram and routine laboratory testing were obtained. Investigators rated pathological gambling symptoms using the SOGS (screening visit only) and the PG-YBOCS (Hollander *et al.*, 1998, 2000). Investigators also rated gambling severity at baseline using the Clinical Global Impression–Severity scale limited to symptoms of pathological gambling (PG-CGI-S) (Guy, 1976). Patients reported severity of pathological gambling symptoms at baseline using the self-rated G-SAS (Kim *et al.*, 2001). Raters were trained in the use of the SCID and other symptom-rating scales before study initiation.

Efficacy and safety assessments

The primary outcome measure was the PG-CGI-I. Clinical response to treatment was defined *a priori* as a PG-CGI-I rating of 1 (very much improved) or 2 (much improved). The PG-CGI-I was performed at weeks 1, 2, 4, 8, 12 and 16.

Secondary outcome measures consisted of: (i) the 10-item total score of the PG-YBOCS (an investigator-completed modification of the YBOCS that rates thoughts/urges of gambling, gambling behaviour, distress and dysfunction related to gambling on a 5-point severity scale; the first five items comprise the urge/thought subscale and items 6–10 refer to gambling behaviour); (ii) the G-SAS total score (a 10-item, self-rated scale designed to assess gambling urges, thoughts, and behaviour during the previous 7 days on a 5-point severity scale); (iii) items 1–4 of the G-SAS (reflecting urge symptoms); and (iv) the investigator-rated PG-CGI-S. The PG-YBOCS and G-SAS were performed at baseline and at study treatment weeks 4, 8, 12 and 16. In addition, the PG-CGI-S was performed at all study visits except the screening visit. Outcome assessments were performed at the time of discontinuation from the study if this was before week 16.

Other assessments performed at baseline and at the end of study treatment weeks 4, 8, 12 and 16 included: (i) the Sheehan Disability Inventory (SDI) (Sheehan, 1983); (ii) the 17-item HAM-D; and (iii) the 17-item HAM-A scale.

Each visit safety assessments included evaluations of weight, sitting blood pressure and heart rate. Adverse effects were documented and included time of onset, duration, severity, action taken and outcome. Use of concomitant medications was recorded in terms of daily dosage, stop and start dates and reason for use. Laboratory assessments (e.g. clinical chemistry, haematology and urinalysis) were performed at initial screening and repeated at week 16 (or at the time of study discontinuation). Compliance was monitored by pill count, and patients were counselled if found to be noncompliant.

Statistical analysis

The main comparison of interest was paroxetine versus placebo in the intent-to-treat (ITT) population. The ITT population comprised all patients who were randomized to double-blind study medication with at least one post-baseline efficacy assessment. Statistical analyses used both a last-observation-carried-forward (LOCF) dataset and the observed-case (OC) dataset.

Baseline characteristics were compared between treatment groups using *t*-tests or chi-square tests (for sex). Efficacy analyses were performed using change from baseline to end-point during the 16-week treatment period. For the primary measure of clinical response to treatment, based on the PG-CGI-I scale, a logistic regression was conducted to test gender, site, treatment group and baseline severity as predictors of treatment response. Because of the possible association between gambling and nicotine use (Smart and Ferris, 1994), chi-square analysis was used to test whether nicotine use was related to response to treatment. Furthermore, given that the previous study with paroxetine demonstrated that gambling urges responded to medication (Kim *et al.*, 2002), chi-square analysis was also performed to examine whether urge severity at baseline was related to treatment response. Secondary efficacy variables were analysed using repeated-measures analysis of variance, with treatment, time and gender in the model and the PG-YBOCS urge scale at baseline as a covariate. Two-sided $P < 0.05$ was considered statistically significant. Treatment–by–site interactions were examined in all analyses.

The number and intensity of adverse events were compared between groups using *t*-tests. The proportion of patients who discontinued treatment because of adverse events and the incidence of clinically significant laboratory abnormalities were compared between treatment groups using Fisher's exact test. Changes in vital signs were compared for the treatment groups using Wilcoxon rank sum test.

Temporal course of response to treatment was examined using a mixed effects model for longitudinal data. Response curves for each treatment group were examined and differences compared. Survival analysis, using the Kaplan–Meier method, was employed to determine whether groups differed in the time to response.

Results

Demographic and clinical characteristics

Of 94 subjects screened, 11 did not meet inclusion criteria. Additionally, seven subjects were deemed placebo responders during the 1-week, placebo lead-in phase. A total of 76 patients (mean age 45.4 ± 10.6 years; 30 women, 46 men) were randomly assigned to paroxetine ($n = 36$) or placebo ($n = 40$), Thirty-four (94.4%) paroxetine-treated patients and 37 (92.5%) placebo-treated patients were available for at least one post-randomization efficacy assessment and thus comprised the ITT population (Table 1). Twenty-one of the 36 patients assigned to paroxetine, and 24 of the 40 patients assigned to placebo, completed all study visits.

For the ITT population, there was a significant difference between the treatment groups with respect to gender for 56% of the active group and 25% of the placebo group women (chi squared = 7.404; d.f. = 1; $P = 0.007$). No

other demographic variables distinguished the treatment groups.

Baseline clinical characteristics are shown in Table 2. The only between group difference at baseline was in the urge/thought subscale score of the PG-YBOCS ($t = 2.132$; d.f. = 63; $P = 0.037$).

Table 1 Demographic data of pathological gamblers randomized to paroxetine or placebo

Characteristic	Paroxetine ($n=36$)	Placebo ($n=40$)
Mean age, years (SD)	47.0 (11.6)	42.0 (15.0)
Sex, *n* (%)		
Female	20 (55.6)	10 (25.0)
Male	16 (44.4)	30 (75.0)
Marital status: *n* (%)		
Single	5 (13.9)	8 (20.0)
Married	21 (58.3)	24 (60.0)
Divorced or separated	9 (25.0)	8 (20.0)
Widowed	1 (2.8)	0 (0)
Ethnicity: *n* (%)		
White	29 (80.6)	36 (90.0)
African-American	3 (8.3)	1 (2.5)
Other	4 (11.1)	3 (7.5)
Education, *n* (%)		
Less than high school	4 (11.4)	7 (18.4)
High school graduate	4 (11.4)	8 (21.1)
Some college or trade school	20 (57.1)	13 (34.2)
College graduate	5 (14.3)	5 (13.2)
Graduate or professional school	2 (5.8)	5 (13.2)
Missing data	1 (2.8)	2 (5.0)
Income		
Less than 20K per year	5 (13.9)	9 (23.1)
20K to 39K	14 (38.9)	7 (17.9)
40K to 59K	11 (30.6)	13 (33.3)
60K to 99K	3 (8.3)	6 (15.4)
100K or over	3 (8.3)	3 (7.7)
Missing data	0 (0)	2 (5.1)

Treatment efficacy

Treatment with paroxetine did not yield significantly greater efficacy than placebo at study end-point as assessed by PG-CGI-I score. As assessed by a score of 1 or 2 on the PG-CGI-I ('very much improved' or 'much improved'), 20 (58.8%) paroxetine-treated subjects and 18 (48.6%) placebo-treated subjects were responders (chi squared = 0.737; d.f. = 1; $P = 0.390$). Of completers, 14 (66.7%) paroxetine-treated and 15 (62.5%) placebo-treated subjects were responders (chi squared = 0.036; d.f. = 1; $P = 0.850$). Week-by-week, the percentage of responders receiving paroxetine was consistently larger than the percentage randomized to placebo, but this difference never reached statistical significance (Fig. 1). Survival analysis also showed that the groups did not differ significantly in their time to response (log rank = 0.74, d.f. = 1, $P = 0.389$).

Assessment of the primary efficacy variable (PG-CGI-I), using a hierarchical logistic regression and controlling for baseline urge/thought subscale of the PG-YBOCS, resulted in a final model with no variables (gender, site, treatment group, PG-CGI-S and PG-YBOCS total score) significantly related to response. Secondary efficacy measures were assessed using repeated measure ANOVA with the PG-YBOCS urge/thought subscale score as a covariate and resulted in no significant response (Table 3). Using random regression analysis with treatment, time and treatment-by-time interaction as predictors (with gender and PG-YBOCS urge/thought subscale score as covariates) of primary and secondary efficacy variables, the results were similar to those using repeated-measures ANOVA (data not shown).

Table 2 Baseline characteristics of pathological gamblers randomized to paroxetine or placebo

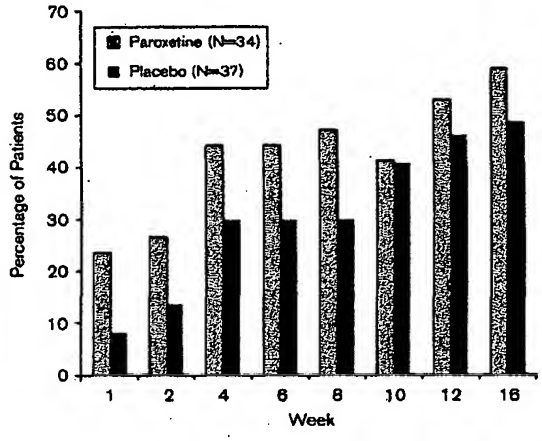
Characteristic	Placebo ($n=37$)		Paroxetine ($n=34$)		Independent samples test		
	Mean	SD	Mean	SD	*t*	d.f.	*P*
PG-CGI-Severity	4.6	0.8	4.9	1.0	1.544	71	0.127
PG-YBOCS Total Score	18.3	3.8	21.7	5.6	1.816	64	0.074
PG-YBOCS Urge/Thought Score[a]	9.5	2.1	10.8	2.6	2.125	66	0.037
PG-YBOCS Behaviour Score[b]	9.2	2.8	10.0	3.2	1.191	64	0.238
G-SAS Total Score	27.3	6.8	31.3	10.3	1.563	70	0.123
G-SAS Urge Score[c]	8.9	2.4	10.7	3.8	1.932	70	0.057
Sheehan Disability Inventory	14.6	6.7	13.8	7.7	−0.742	71	0.461
Hamilton Depression[d]	5.2	4.5	6.0	3.5	0.909	70	0.366
Hamilton Anxiety[e]	4.3	3.9	5.3	3.7	1.345	70	0.183

Only those subjects with one post-randomization visit were included. PG-CGI, Clinical Global Impression scale (improvement) for symptoms of pathological gambling; PG-YBOCS, Yale–Brown Obsessive–Compulsive Scale Modified for Pathological Gambling; G-SAS, Gambling Symptoms Assessment Scale.
[a]Refers to items 1–5 on the PG-YBOCS which include time occupied, interference, distress, resistance and degree of control of thoughts/urges.
[b]Refers to items 6–10 on the PG-YBOCS which include time occupied, interference, distress, resistance and degree of control of gambling behaviour.
[c]Refers to items 1–4 on the G-SAS that reflect urge frequency, intensity, duration, and degree of control.
[d]Hamilton Depression Rating Scale (17-item version).
[e]Hamilton Rating Scale for Anxiety (17-item version).

Subjects with severe or extreme urges to gamble were no more likely to be responders than those with mild or moderate urges. Nineteen paroxetine-treated subjects and 11 placebo-treated subjects reported severe or extreme urges to gamble at baseline (corresponding to a score of 3 or 4 on Item 1 of the G-SAS). Of 19 paroxetine-treated subjects with severe or extreme urges at baseline, 11 (57.9%) were responders using PG-CGI-I score of 1 or 2, compared with nine (60.0%) paroxetine-treated subjects with mild or moderate urges (chi squared = 0.015; d.f. = 1; $P = 0.901$). Of 11 placebo-treated subjects with severe or extreme urges, five (45.5%) were responders compared to 13 of the 25 placebo-treated subjects (52.0%) with mild or moderate urges (chi squared = 0.131; d.f. = 1; $P = 0.717$).

Tobacco use did not correlate with response to paroxetine. Forty-five (59.2%) of the randomized subjects were smokers (20 randomized to paroxetine, 25 to placebo). These 45 subjects smoked a mean number of 25.0 ± 13.0 cigarettes per day. Of the 45 subjects who used nicotine, 12 (60.0%) of those randomized to paroxetine were responders (PG-CGI-I score of 1 or 2) compared to 11 (44.0%) of the smokers randomized to placebo (chi squared = 1.138; d.f. = 1; $P = 0.286$).

Fig. 1



Percentage of patients achieving response (PG-CGI-I Score of 1 or 2) during treatment of pathological gambling with paroxetine or placebo.

Nineteen (63.3%) of the paroxetine-treated subjects and 16 (50.0%) of the placebo-treated subjects achieved a 30% or greater reduction on total PG-YBOCS score by study endpoint (chi squared = 1.120; d.f. = 1; $P = 0.290$). Week-by-week, there was a significant treatment by time interaction in PG-YBOCS scores between groups at week 4 ($F = 6.58$; d.f. = 1; $P = 0.013$), but this difference was not sustained by week 8 ($F = 3.64$; d.f. = 1; $P = 0.062$).

Analysis of the percentage reduction in total PG-YBOCS score from baseline to endpoint did not yield a significant between group difference at study endpoint ($t = -0.071$; d.f. = 53; $P = 0.944$). Although the percentage reduction in total G-SAS score (36.1%) was of greater magnitude in the paroxetine-treated subjects compared to the placebo-treated subjects (18.1%), the difference did not reach statistical significance ($t = -1.744$; d.f. = 59; $P = 0.086$).

Week-by-week analysis demonstrated an overall treatment by time interaction on the G-SAS urge subscale which achieved statistical significance at week 4 ($F = 6.60$; d.f. = 1; $P = 0.013$) and at week 12 ($F = 8.59$; d.f. = 1; $P = 0.005$) compared to baseline. Week-by-week analysis of overall functioning using the SDI demonstrated no statistical differences.

Tolerability

Paroxetine was well tolerated. The paroxetine and placebo groups reported mean numbers of 7.7 (6.1) and 4.6 (5.0) adverse events per subject, respectively. The between group difference was statistically significant ($t = -2.32$; d.f. = 69; $P = 0.023$). The intensity of adverse events and rates of study discontinuation did not significantly differ between groups. Fifteen (41.7%) paroxetine subjects discontinued compared to 16

Table 3 Treatment outcome of pathological gamblers randomized to paroxetine or placebo

Measures	Paroxetine ($n = 34$)				Placebo ($n = 37$)				ANOVA		
	Baseline		Endpoint		Baseline		Endpoint		F	d.f.	P
	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
PG-YBOCS	21.7	5.6	13.9	9.9	18.3	3.8	12.4	7.6	0.43	1	0.513
G-SAS	31.3	10.3	20.2	12.4	27.3	6.8	21.3	9.9	1.51	1	0.224
G-SAS Urge	10.7	3.7	6.7	4.0	8.9	2.4	7.1	3.3	1.90	1	0.174
SDI	13.8	7.7	8.4	7.0	14.8	6.7	9.1	8.1	0.66	1	0.418

Last-observation-carried-forward (LOCF) analysis of measures of response based on repeated-measures analysis of variance with the PG-YOBCS urge/thought subscale score as covariate. PG-YBOCS, Yale–Brown Obsessive–Compulsive Scale Modified for Pathological Gambling; G-SAS, Gambling Symptoms Assessment Scale; G-SAS Urge, Items 1–4 of the Gambling Symptom Assessment Scale; SDI, Sheehan Disability Inventory.

(40.0%) placebo subjects (chi squared = 0.022; d.f. = 1; $P = 0.883$), and six (16.7%) of the paroxetine subjects and one (2.5%) placebo patient withdrew due to adverse events. The most common adverse events in the paroxetine group were dry mouth ($n = 8$; 22.2%), headache ($n = 7$; 19.4%) and nausea ($n = 5$; 13.9%). Significant changes in laboratory parameters or vital signs were not observed during the study.

Discussion

This first multi-centre trial of a medication in the treatment of pathological gambling assessed pharmacological response in a large sample of patients from multiple geographical sites and demonstrated an overall response rate of 59% among those treated with paroxetine, with an almost equally robust response by subjects assigned to placebo (49%). There was no evidence of statistically significant advantage for paroxetine on any of the outcome measures.

A previous double-blind study of paroxetine found the drug efficacious in treating pathological gambling (Kim *et al.*, 2001). In the present study, paroxetine substantially reduced pathological gambling symptoms during 16 weeks of active treatment, but the overall response was comparable to placebo. The placebo-treated subjects exhibited a steady improvement in gambling symptoms over the course of 16 weeks. The present study therefore differs from the previously published paroxetine treatment study in which an initial placebo response diminished over the latter part of the study. This difference could, in part, account for the conflicting findings from previous reports of the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of pathological gambling. Further studies are required to determine the reason for symptom improvement in both subject groups (for example, frequency of contact with a patient).

A 6-month, placebo-controlled study of fluvoxamine also failed to demonstrate the superiority of drug treatment to placebo for pathological gambling (Blanco *et al.*, 2002). However, the observation of apparent discordant findings in drug response is not unique to pathological gambling. For example, differences in response to drug treatment have been observed in other patient groups such as depressed patients (Walsh *et al.*, 2002) or alcohol dependent subjects receiving naltrexone (O'Malley *et al.*, 1992; Krystal *et al.*, 2001). More studies are needed to investigate the reasons for the differences and to determine the efficacy of paroxetine and other SSRIs in the treatment of pathological gambling.

The reasons for the high placebo response rate in this study are unclear. The placebo response would indicate that nonspecific factors had beneficial effects. First, impulse control disorders may be characterized by a tendency to reduce unwanted behaviours when greater attention is focused on them. Asking subjects to be more aware of their behaviours may have served the function of covert cognitive behavioural therapy, an intervention with demonstrated benefits in pathological gambling (Petry and Roll, 2001). Second, the motivational states of the subjects may have influenced response. Although motivation was not assessed in the present study, the data suggest that patients in the preparation (action) or maintenance/relapse prevention phases are more motivated to change their behaviour than those patients in the denial or precontemplation and contemplation phases (DiClemente *et al.*, 1991). Finally, the strength of a therapeutic connection made between a study subject and the investigator may influence response to treatment (e.g. the subject may not want to disappoint the investigator by continuing to gamble).

Tolerability of paroxetine in pathological gamblers did not differ significantly from tolerability reported in other disorders (Lesieur and Blume, 1987; Gunasekara *et al.*, 1998). Of those treated with paroxetine, 16.7% dropped out because of adverse events, and it is possible that some of the 25% (9/36) of the paroxetine population lost to follow-up may also have stopped participation because of adverse events.

This study suffers from several limitations. First, the existence of baseline between-group differences (gender, urge/thought subscale of the PG-YBOCS) may have influenced differences in treatment outcome. Second, the sample of pathological gamblers may not reflect the larger population of people with the disorder. Pathological gambling has high rates of comorbidity with mood, anxiety, and substance use disorders (McCormick *et al.*, 1984; Black and Moyer, 1998). Our study excluded patients with these disorders and may have limited generalizability to a larger population of people with pathological gambling. Third, the moderate sample size may have precluded the identification of treatment outcomes between groups. Paroxetine consistently resulted in a greater percentage of responders at each study visit, and a greater percentage of paroxetine-treated subjects achieved a 30% or greater reduction on the PG-YBOCS by study endpoint. Although the PG-YBOCS failed to show a significant treatment by time interaction for paroxetine by week 8, there was still a trend towards significance ($P = 0.062$). Such trends in a small sample may suggest that a larger study might well register a significant difference. Given the inconsistent findings from previous trials of SSRIs in the treatment of pathological gambling, the question of whether a larger sample would have detected differences between paroxetine and placebo deserves further examination. Controlled studies in larger samples of patients with

pathological gambling and comorbid disorders are necessary to test medications under more naturalistic conditions.

There are currently no Food and Drug Authority approved treatments for pathological gambling. Although paroxetine treatment was associated with an earlier response, paroxetine- and placebo-treated groups demonstrated comparable overall improvement. Further studies are needed to determine the extent to which these gains are maintained over time within each group, and the mechanism underlying the improvements.

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